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The American Heart Journal

VOL. 12 SEPTEMBER, 1936 No. 3

Original Communications

THE USE OF CIRCULATORY MEASUREMENTS IN EVALUATING PULMONARY AND CARDIAC FACTORS IN CHRONIC LUNG DISORDERS*

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INTRODUCTION

THE clinician is not infrequently faced with the problem of differentiating between pulmonary and cardiac insufficiency. The problem presents difficulties unless accessory means are employed to evaluate the genesis of the symptoms presented by the patient.

It is known that the symptoms of pulmonary insufficiency may closely resemble the cardinal symptoms of myocardial failure, i.e., cyanosis, exertional dyspnea, orthopnea, cough, and diminished vital capacity. The accentuated second pulmonic sound also may be a manifestation of either condition. The paroxysmal nature of bronchial asthma often renders it indistinguishable from the asthma that attends left ventricular failure. Even greater confusion arises in those cases in which combined cardiac and pulmonary insufficiency contribute to the pathogenesis of the presenting symptoms. From a diagnostic, prognostic, and therapeutic standpoint, it therefore becomes important in these cases to evaluate the rôle of pulmonary and cardiac factors in the cardiopulmonary derangement. When the clinical picture is not due to pulmonary disease alone, it is also necessary to establish whether the heart failure is secondary to the pulmonary disorder or independent of it.

Clinical methods have failed to give a clear picture of the altered circulatory dynamics in chronic pulmonary disease. Because of its lesser circulatory obligations, the right heart possesses a large physiological factor of safety which enables it to cope adequately with extensive disease of the pulmonary vascular bed. Isolated failure of the right side of the heart may nevertheless occur, and, when it does, this condition is frequently first suspected by the pathologist. Pathological studies, however, have also been unsatisfactory in elucidating

*From the Medical Services and Laboratories of the Mount Sinai Hospital.

the effect of chronic lung disorders on cardiovascular dynamics. For example, the finding of right ventricular hypertrophy and dilatation at the post-mortem table does not necessarily imply that the right heart has failed. It may simply mean that the right heart has conditioned itself to the load thrown upon it by the increased pulmonary resistance, this mechanism being analogous to that in essential hypertension in which hypertrophy and dilatation represent similar compensatory adjustments of the left side of the heart to an increased systemic resistance. The application of circulatory measurements has been a real step forward in the attempt to understand the pathological physiology of the heart and circulation in emphysema and other chronic lung disorders. Weiss and Blumgart[1] made pioneer observations in this field. These authors, employing the radium C method, and Tarr, Oppenheimer, and Sager,[2] using the decholin method of studying blood flow through the lungs, observed that in uncomplicated emphysema the rate of circulation through the lungs was within the limits of normal.

Because of these observations this study was undertaken to note the effect of chronic pulmonary conditions upon the circulatory dynamics and to present relatively simple means of differentiating between cardiac and pulmonary insufficiency. Cardiac output determinations were not deemed feasible because such measurements not only require a complicated laboratory set-up, but they postulate normal gaseous exchange. Gas analyses of arterial and venous blood, which are laborious procedures, and vital capacity measurements were not employed in our observations because deviations from the normal would by themselves not have any significant differential value.

Clinical Material.—One hundred and two patients with clinical and roentgenographic evidence of chronic pulmonary disease were observed. Of these, 54 cases of bronchogenic (obstructive) emphysema and 16 cases of bronchial asthma were employed as the basis of this communication.

METHODS

A. The Initial Venous Pressure.—This was determined in an antecubital vein by the direct method of Taylor, Thomas, and Schleiter,[3] modified by moistening the interior of the manometer with 10 per cent sodium citrate.

B. Right Upper Abdominal Compression.—Historically, William Pasteur[4] in 1885 seems to have been the first to describe swelling, with or without pulsation, of the jugular vein as the result of pressing upon the engorged liver; he considered this a sign of tricuspid regurgitation. Subsequently Rondot[5] obtained this phenomenon in a variety of circulatory disturbances which we now regard as insufficiency of the right heart; he called it the hepatojugular reflux. Plesch[6] noted the absence of this phenomenon in patients whose right ventricles were still capable of accommodation, and considered the presence of this sign to be of ominous significance. Because this maneuver appeared to be

an additional aid in studying the functional efficiency of the right ventricle, Fishberg and Hitzig[7] employed it in their observations on several hundred patients suffering from a variety of circulatory and noncirculatory conditions. In addition to observing clinically the filling of the cervical veins, they carried out objective measurements of the rise of the venous pressure in centimeters of blood during one minute of sustained right upper abdominal compression. This manometric measurement has definite advantages over simple clinical observations as employed by the older clinicians for the following reasons: First, it is often difficult to judge on clinical grounds the presence of increased distention of the external jugular veins, unless there is manifest failure of the right side of the heart. Second, the clinical method of evaluating the distention of the cervical veins offers difficulties in patients whose external jugular veins are hidden by a thick panniculus or whose veins are excessively prominent or gaping either normally or as a result of phlebosclerosis or other degenerative changes. Third, it permits detection of lesser grades of cervical distention, not grossly demonstrable, and also gives quantitative data for comparative observations. Fourth, it enables registration of a fall of the venous pressure—a phenomenon frequently encountered in normal individuals.

TABLE I

VENOUS PRESSURE DETERMINATIONS

	INITIAL VENOUS PRESSURE (CM. OF BLOOD)	VENOUS PRESSURE AFTER ONE MINUTE OF R.U.Q. COMPRESSION (CM. OF BLOOD)
In health	4-8	No rise, or fall of ½ to 2 cm.
In latent or incipient right ventricular insufficiency	4-8-10	1 to 5 cm. rise
In frank right heart failure	Above 8-10	5 to 20 cm. rise

The first column of Table I shows the initial venous pressure measured in an antecubital vein. In normal individuals the venous pressure ranges from 4 to 8 cm. of blood. By pressing over the right upper quadrant for a period of approximately one minute, the venous pressure level in the antecubital vein of normal individuals either remains stationary or eventually falls progressively from 0.5 to 2 cm. provided they breathe as usual and do not tense their muscles. The delayed fall may be explained on the basis of a subsequently diminished venous return due to temporary compression of the inferior vena cava and portal system of veins. In incipient right heart failure, in which the initial venous pressure is either normal or slightly elevated to about 10 cm., a rise of 1 to 5 cm. may occur after one minute of right upper quadrant compression. In frank right heart failure in which the initial venous pressure is considerably above 8 to 10 cm., a rise of 5 to 20 cm. above the original level of venous pressure may be obtained after right upper

quadrant compression. This maneuver is of clinical value since it demonstrates the inability of the right ventricle to take care of the temporary increase of the venous return. It is true that the filling of the cervical veins may be discernible clinically, but these measurements serve to bring out slight disturbances in the functional capacity of the right heart even in the presence of a normal initial venous pressure. That this phenomenon is not merely a "liver" phenomenon, as was regarded by the older clinicians, may be proved by demonstrating similar rises in venous pressure in right heart failure when the left lower quadrant is compressed. This indicates that this so-called liver stasis phenomenon depends primarily upon the elevation of intraabdominal pressure and the resulting increased venous return.

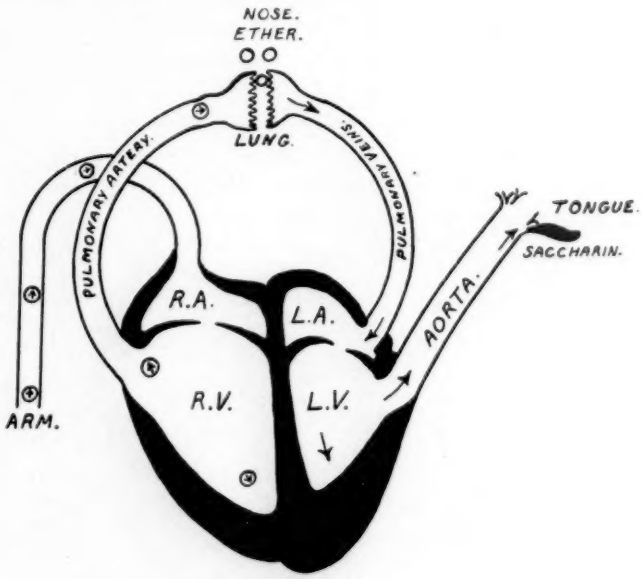

Fig. 1.

C. *Circulation Time.*—1. Arm-to-lung time (ether).

2. Arm-to-tongue time (saccharin or decholin).

3. Lung-to-tongue time (saccharin time minus ether time).

The circulation time from arm to lung is determined by intravenous injection of 5 minims of ether mixed with 5 minims of normal saline. Normally this ranges between 3.5 and 8 sec.[9] The velocity of blood flow from the arm to the tongue is determined by the intravenous injection of saccharin (2.5 cm. in 2.5 c.c. of water) or of 3 to 5 c.c. of 20 per cent solution of sodium dehydrocholate, called decholin.[2] The arm-to-tongue time is normally from 9 to 16 sec.[12] The lung-to-tongue time is determined indirectly by subtracting the ether time from the saccharin time; this is normally between 4.5 and 10 sec. (see Table II and Fig. 1).

The arm-to-lung time may be regarded as a rough measure of the ability of the right heart to maintain a normal velocity of blood flow through its afferent and efferent vessels. The lung-to-tongue time represents a similar function of the left ventricle. Retardation of the rate of flow in the arm-to-lung or lung-to-tongue segments is indicative of functional insufficiency of the corresponding chamber of the heart.

TABLE II

	NORMAL VALUES (SEC.)
Arm-to-lung time (ether time)	3.5- 8
Arm-to-tongue time (saccharin or decholin time)	9.0-16
Lung-to-tongue time (saccharin time minus ether time)	4.5-10

D. The Blood volume was determined by the Congo red method in twenty-one patients suffering from emphysema. As it was evident early in the investigation that these determinations offered little of value in differentiating pulmonary from myocardial insufficiency, these measurements were therefore abandoned in the remainder of the series.

Circulatory Criteria for Determining the Functional Capacity of the Right Ventricle in Chronic Pulmonary Disease (Table III)

This study was undertaken to determine the presence or absence of circulatory disturbances in patients suffering from varying degrees of

TABLE III

CIRCULATORY CRITERIA OF FUNCTIONAL EFFICIENCY OF RIGHT VENTRICLE IN CHRONIC PULMONARY DISEASE

	NORMAL	INCIPIENT ISOLATED RIGHT HEART FAILURE	FRANK ISOLATED RIGHT HEART FAILURE
Initial venous pressure	4-8 cm.	4.5-8 or 10 cm.	Over 10 cm.
R.U.Q. compression	0 or fall	1-5 cm. rise	5-20 cm. rise
Arm-to-lung time	3.5″ to 8″	Normal or slight +	+
Lung-to-tongue time	4.5″ to 10″	Normal	Relatively normal

pulmonary insufficiency. Although chronic pulmonary disorders may cause hypertrophy of the right ventricle, the so-called cor pulmonale, the functional capacity of this chamber may not be impaired, and the patient suffers from symptoms of isolated pulmonary insufficiency. In these patients, the functional efficiency of the right ventricle is indicated by the presence of the following:

A. A normal venous pressure.
B. The absence of a rise of venous pressure on right upper quadrant pressure.
C. A normal ether time.

In cases, however, in which the peripheral resistance of the lungs is either of long standing or of high grade, slight impairment of the functional efficiency of the right ventricle may be detected by employing two criteria:—

TABLE IV

BRONCHOGENIC (= OBSTRUCTIVE) EMPHYSEMA

		I. PULMONARY INSUFFICIENCY ± COMPENSATED COR PULMONALE	II. PULMONARY AND MYOCARDIAL INSUFFICIENCY			
			A. INCIPIENT ISOLATED RIGHT HEART FAILURE	B. ISOLATED RIGHT HEART FAILURE	C. LEFT HEART FAILURE ± INCIPIENT RIGHT HEART FAILURE	D. UNIVERSAL HEART FAILURE
No. of cases		25	4	7	14	4
Cyanosis		17	4	7	12	4
Polycythemia		12	2	3	3	0
Cardiovascular complications		13	0	2	12	4
Acute pulmonary complications		0	0	4	0	1
Initial venous pressure	subnormal	5	0	0	2	0
	normal	20	4	0	12	0
	high	0	0	7	0	4
R.U.Q. compression	no rise of V.P.	25	0	0	3	0
	rise of V.P.	0	4	7	10	4
Arm-to-lung time	normal	24	3	0	9	0
	prolonged	1	1	7	5	4
Arm-to-tongue time	normal	25	4	0	0	0
	prolonged	0	0	6	14	4
Lung-to-tongue time	normal	25	4	6	0	0
	prolonged	0	0	0	14	4
Blood volume	normal	9	–	1	3	–
	increased	2	1	1	3	1
Electrocardiogram	R.V.P.	3	3	4	2	0
	L.V.P.	6	0	1	3	0
Deaths		1	0	4	2	2

A. A rise in the venous pressure on right upper quadrant compression in spite of the presence of a normal or a slightly elevated initial venous pressure.

B. A normal or slightly prolonged ether time.

When the functional capacity of the right ventricle is grossly impaired, due to extreme reduction of the patency of the pulmonary vascular bed or extreme fatigue of the right ventricular myocardium, a circulatory disturbance which may be regarded as isolated failure of the right heart may be produced. It is noteworthy that in these patients, although there is systemic congestion, there is no congestion in the lungs, the latter condition being characteristically found in disturbances associated with failure of the left side of the heart. The circulatory criteria for frank heart failure of the right ventricle are:

A. Elevated initial venous pressure.

B. Marked rise on right upper quadrant pressure.

C. Prolongation of the ether time except in rare instances.

D. A normal or relatively normal lung-to-tongue time, the most characteristic finding of isolated right heart failure in contradistinction to right heart failure that follows insufficiency of the left side of the heart.

Emphysema.—With these criteria in mind, fifty-four cases of bronchogenic (or so-called obstructive) emphysema were studied. On the bases of clinical features and circulatory measurements, these cases were divided into two distinct groups (Table IV).

1. The first group, which consisted of twenty-five patients, presented no circulatory disturbances. The venous pressure, both initial and after right upper quadrant compression, was normal. The arm-to-lung and the arm-to-tongue times were within normal limits. In addition to the presence of right ventricular hypertrophy demonstrated by x-ray examination and the electrocardiogram, there were also cardiovascular complications in thirteen patients of the series. An important finding in this group is the definite absence of a high venous pressure. In five patients of our series, subnormal venous pressures were actually obtained. In a few cases, showing a marked degree of cyanosis and polycythemia, fast normal circulation times were obtained. This is a significant observation in agreement with the work of Cloetta.[8]

2. The second large group consisted of cases in which pulmonary and myocardial insufficiency coexisted. These cases were subdivided into four groups. The first two groups included cases in which the myocardial insufficiency was secondary to disease of the lung, whereas in the last two groups the heart failure was an incidental complication probably resulting from disease of the left side of the heart. In these latter two groups, when the right heart also failed (incipient or frank failure), it was probably on the basis of marked hypertension of both arms of the pulmonary circuit, due to the combined influence of pulmonary disease and left ventricular insufficiency.

A. Incipient failure of the right heart was observed in four cases. Although these patients presented many of the symptoms and signs of circulatory failure such as cyanosis, orthopnea, and dyspnea, the circulatory measurements were not significantly disturbed. The only consistent abnormality was the presence of a rise of the normal initial venous pressure after right upper quadrant compression. In one case out of the four, there was also retardation of the arm-to-lung time. Otherwise the blood velocity studies were within normal limits. These findings indicate that, although there may be a marked reduction in the cardiac reserve as manifested by the right upper quadrant compression, the other circulatory measurements (venous pressure and circulation times) may be maintained within the normal range.

B. Frank isolated right heart failure was observed in seven patients. In all of these patients many of the characteristic clinical features of right heart failure, such as venous engorgement, enlargement of the liver, cyanosis, ascites, and peripheral edema, were observed. The initial venous pressure was elevated in all cases. On right upper quadrant compression the blood column in the manometer rose from 5 to about 15 cm. above the initial venous pressure level. The arm-to-lung and arm-to-tongue times were prolonged. The lung-to-tongue time, however, fell within the normal range, indicating that slowing of the blood flow was predominantly in the segment between arm and lung. The normal lung-to-tongue time in the presence of a high initial venous pressure and a prolonged ether time appeared to be pathognomonic of isolated failure of the right heart secondary to emphysema.* This finding is consistent with the absence of pulmonary venous congestion and is indicative of a normal or a relatively better functioning left ventricle. Although there was prolongation of the arm-to-tongue time, there appeared to be no parallelism between the degree of slowing of the blood flow through the lung and the severity of the clinical symptoms, an observation which has previously been made by Blumgart. The symptoms in these patients are probably on a twofold basis: (1) primary disease of the lung,† i.e., pulmonary insufficiency which is the predominant factor, and (2) the slowing of the blood flow through the right heart unit. It is also of interest that in this group four of the seven patients died. In some of these cases death was attributed to right heart

*It has been suggested that the large amount of residual air in emphysema causes an artificial delay in the passage of ether from the pulmonary capillaries to the nose which may really account for the normal or relatively normal lung-to-tongue time. The latter, which represents the difference between the saccharin and the ether times, is therefore shortened erroneously. This criticism may be refuted by the following observations. First, cases of advanced emphysema, not complicated by right heart failure, yielded normal arm-to-lung times, despite the undoubted presence of excessive residual air. Second, in several instances of severe bronchial asthma, in which a high residual air capacity was undoubtedly present, the arm-to-lung time was normal and almost identical in the acute attack and in the asthma-free interval.

†Under primary disease of the lung are included the secondary effects of the pulmonary disorder upon the patency of its vascular bed, the elasticity of the lung, and the intrapleural pressure. That the resulting decreased negativity of the normal intrapleural pressure plays a rôle in the production of some of the phenomena in pulmonary emphysema has been suggested by the original work of Kountz, Alexander and Dowell.[11]

failure. At post-mortem examination, however, acute bronchopulmonary complications were found. In view of only slight slowing of the circulation time through the pulmonary pathway in these patients, it appears more likely that death was caused by acute increase of the pulmonary insufficiency when the acute bronchopulmonary complication was added to the original condition.

C. Left heart failure with or without incipient right heart failure was observed in fourteen patients. In this group unrelated cardiovascular complications were present in twelve cases and lacking in the remaining two. This finding was probably incidental, inasmuch as many of these patients with emphysema are in the age group where degenerative diseases of the cardiovascular system are prevalent. This classification of the cases with left heart failure was based on the observation of Hitzig, King, and Fishberg[9] in isolated failure of the left ventricle, who found that the venous pressure was normal, that the ether (arm-to-lung) time was usually normal but might be slightly retarded, and that the saccharin (arm-to-tongue) time was usually prolonged. The initial venous pressure in this group was subnormal in two patients, and within the normal range in twelve patients. On right upper quadrant compression, the venous pressure level remained stationary in three patients and rose in ten patients. The arm-to-lung time was normal in nine patients and slightly prolonged in five. The arm-to-tongue time was considerably prolonged in all these patients. The outstanding circulatory disturbance in this group was the presence of consistent prolongation of the lung-to-tongue time. This disturbance was undoubtedly on the basis of left ventricular insufficiency and unrelated to the primary pulmonary disease.

D. Universal heart failure was observed in four patients. All four patients were severely incapacitated. Cardiovascular complications were present in all. The circulatory disturbance probably began with insufficiency of the left ventricle, which, by adding to the burden of an already overstrained right ventricle due to pulmonary disease, led to universal failure of the heart. The initial venous pressure was high in all cases. Right upper quadrant compression caused an enormous rise of the venous pressure level. The arm-to-lung, arm-to-tongue, and lung-to-tongue times were all prolonged. Although the slowing of the blood velocity through the lungs was far greater in this and the previous group than in the group with pure right heart failure, the severity of the clinical symptoms appeared to be no greater in these two groups than in cases due to pure right heart failure (group B).

To summarize the results of circulatory measurements in this group of patients with emphysema, it may be said that, although the right ventricle hypertrophied and dilated in response to the increased work which confronted it in pulmonary emphysema, the circulatory measurements were not prolonged in twenty-five of the fifty-four patients

studied. This is in line with observations of Kountz, Alexander, and Prinzmetal,[10] who concluded that the heart is affected in the majority of patients with emphysema, and that the cardiac lesion, hypertrophy and dilatation of the right ventricle, may produce symptoms, but probably has no clinical reflection in its earlier stages. This work-hypertrophy of the right ventricle may be regarded as the compensated phase of the so-called cor pulmonale. When the work demanded of the right heart exceeds its functional capacity, failure supervenes and gives rise to the so-called decompensated phase of the cor pulmonale. This disturbance was observed in eleven patients of our series. According to the degree of failure and circulatory measurements, we designated four as suffering from *incipient* isolated failure of the right heart, and seven from *frank* isolated failure of the right heart. In eighteen of the patients, who also suffered from combined myocardial and pulmonary insufficiency, the circulatory disturbance probably originated in a majority of instances as a result of unrelated cardiovascular complications which caused either insufficiency of the left ventricle or universal failure.

Bronchial Asthma (*Table V*).—Sixteen patients suffering from bronchial asthma were studied. In all of these patients, emphysema of moderate or marked degree was also present. The circulatory measurements were carried out in all cases during an asthmatic seizure. In twelve of the patients venous pressure determinations were normal; circulation times, however, were either fast normal or average normal. In one of these twelve cases the arm-to-tongue time was even faster than nor-

TABLE V

CIRCULATORY MEASUREMENTS IN ASTHMATIC SEIZURES OF BRONCHIAL ORIGIN
(INFECTIOUS AND ALLERGIC ASTHMA)

CASE	INITIAL VENOUS PRESSURE (CM. OF BLOOD)	RISE AFTER R.U.Q. COMPRESSION (CM. OF BLOOD)	ARM-TO-LUNG TIME (SEC.)	ARM-TO-TONGUE TIME (SEC.)	LUNG-TO-TONGUE TIME (SEC.)
1-11	4 to 8	0	4 to 7	8 to 14	4 to 8.25
12	3.5	0.75	5	7.2	2.2
13*	7.5	2.50	8	12.0	4.0
14*	5.5	1.50	4	12.0	8.0
15*	8.0	2.00	7	15.0	8.0
16†	15.5	7.50	12	20.0	8.0

*Cases showing incipient right heart failure.
†Only case showing frank right heart failure.

CIRCULATORY MEASUREMENTS IN ASTHMATIC SEIZURES OF CARDIAC ORIGIN
(LEFT VENTRICULAR INSUFFICIENCY)

INITIAL VENOUS PRESSURE (CM. OF BLOOD)	RISE AFTER R.U.Q. COMPRESSION (CM. OF BLOOD)	ARM-TO-LUNG TIME (SEC.)	ARM-TO-TONGUE TIME (SEC.)	LUNG-TO-TONGUE TIME (SEC.)
6	1	5½	20	14½
8	6	6	28	22
7	4	8	25	17
10	5	9	21	12
7	3	7	24½	17½

mal. In this case when the circulatory measurements were repeated two days after the asthmatic attack had subsided, the results were practically identical with those obtained during the asthmatic seizure. In two other cases, however, the circulation time was faster during the attack of asthma than in the asthma-free interval. Two of these twelve patients died a few days after the normal measurements were obtained; their deaths were apparently due to severe pulmonary insufficiency rather than to heart failure. The necropsy revealed in one case acute suppurative bronchopneumonia, acute putrid and ulcerative bronchitis and cylindrical bronchiectases, and in the second case in which a condition of status asthmaticus prevailed until death, mucous plugs were found occluding all bronchi. Of the remaining four cases, three showed evidence of incipient right heart failure as determined by right upper quadrant compression, and the fourth presented the circulatory dynamics of frank isolated right heart failure, this patient dying two days after the measurements were taken.

Cardiac Asthma.—The dyspneic states which frequently accompany chronic bronchopulmonary disease, but particularly bronchial asthma, may closely simulate attacks of cardiac asthma. Although it is well known that paroxysms of wheezing dyspnea in bronchial asthma are primarily due to pulmonary disease with the heart participating only secondarily, because of the increased pulmonary resistance, one often finds it difficult to differentiate these paroxysms from true cardiac asthma in which a pathological process originates in the left side of the heart and involves the lung only secondarily. In spite of the fact that clinical differentiation may frequently be made on the basis of disproportionate cyanosis, secondary polycythemia, the presence of clubbed fingers, a history of allergy and chronic cough, x-ray and electrocardiographic evidence of right ventricular preponderance, this differentiation is not always possible. In such patients, circulatory measurements may be invoked as an aid in the differential diagnosis. This is best exemplified in an analysis of the results obtained in five cases of cardiac asthma, secondary to hypertensive and arteriosclerotic disease of the heart, and also by a comparison of these results with those obtained in bronchial asthma (Table V). The venous pressures were normal in four patients and slightly elevated (to 10 cm.) in the fifth patient. In all patients there was a rise of the venous pressure level of 1 to 6 cm. on right upper quadrant compression. The arm-to-lung time was normal in four, and only slightly prolonged in the fifth case. The arm-to-tongue time, and the lung-to-tongue time were considerably prolonged in all patients. The chief difference between the asthma of bronchogenic and that of cardiac origin is that in the former the circulatory measurements are practically normal, while in the latter there is a consistent rise of venous pressure on right upper quadrant compression and a slowing of the circulation through the lungs exhibited particularly by significant

prolongation of the lung-to-tongue time. However, an occasional case of bronchial asthma associated with heart failure may be observed as is demonstrated in one case (Case 16) in which there was a high initial venous pressure and a rise of venous pressure on right upper quadrant compression. Although the arm-to-lung time was prolonged to 12 seconds, the lung-to-tongue time which was within the normal range, served to differentiate it from true cardiac asthma of left ventricular origin. .

Pneumoconiosis, Silicosis and Pulmonary Fibrosis.—Circulatory measurements were also carried out in three cases of pneumoconiosis, in one case of severe interstitial fibrosis of both lungs, and in one case of markedly advanced pulmonary silicosis. One may summarize the results by stating that no abnormalities in the circulatory dynamics were recorded in these five cases.

COMMENT

The fundamental disturbances in chronic pulmonary disease of the type described in this paper are of twofold nature. One is the altered property of the alveolar walls which interferes with adequate aeration of blood in its passage through the lungs and gives rise to anoxemia. The other is the mechanical reduction in the patency of the pulmonary vascular bed. This latter condition heightens the pulmonary peripheral resistance and leads to a circulatory condition known as hypertension of the pulmonary circuit, which has been popularized by the writings of Moschcowitz.[13] As we shall see later, both of these factors, namely the anoxemia and the pulmonary peripheral resistance, probably play important rôles in the genesis of failure of the right heart in chronic pulmonary disease. Although there is considerable experimental evidence which indicates that the right heart, under ordinary conditions, possesses a large physiological factor of safety, yet instances of isolated failure of the right heart in chronic lung disorders are not infrequently observed. What factors operate in chronic pulmonary disease to cause fatigue and failure of the right ventricle?

The right ventricle performs work in transporting blood through the pulmonary channels to the left side of the heart. The amount of work performed by the right ventricle is determined by the volume of blood it has to propel (venous return) and the pulmonary resistance against which its venous load is ejected. As has been shown by Cloetta,[8] the degree of distention of the lungs also determines in a great measure whether the pulmonary vascular resistance is decreased or augmented. Unless a teleological explanation could be substituted, it is probable that the rapid circulation times in some cases of asthma with emphysema actually result from a reduction in the resistance to blood flow through the lungs. In the majority of instances of emphysema, however, the pulmonary vascular resistance becomes augmented, and the work done by the right ventricular chamber is consequently proportionately in-

creased. As a consequence, even in the early stages of chronic pulmonary disease, the heart may hypertrophy (and even dilate) as a physiological response to increased work. This work-hypertrophy of the right heart, designated in the literature as cor pulmonale, enables it to cope adequately with the increased work which confronts it. The circulation through the lungs is thereby maintained at a normal or fast normal speed, and the organism suffers solely from the effects of the primary pulmonary disease and the associated anoxemia.

Recent acute experiments by Fineberg and Wiggers[14] have established a definite relationship between reduction of the functional capacity of the right ventricle and the degree of narrowing of the pulmonary vascular bed. It appears that considerable reduction of the pulmonary vascular bed is necessary before the blood supply to the left side of the heart suffers and arterial pressures decrease. Tigerstedt[15] quotes earlier experiments which indicate that between one-half and two-thirds of the pulmonary branches can be ligated in animals before significant reduction in the mean arterial pressure takes place. Haggart and Walker,[16] and Gibbon, Hopkinson and Churchill[17] found that the lumen of the pulmonary artery could be reduced approximately 60 per cent without reducing the arterial pressure. Recently Fineberg and Wiggers[14] studied the reactions of the right ventricle to graded compression of the pulmonary artery with the aid of optical manometers. By simultaneous registration of right intraventricular and aortic pressures, these authors observed the compensatory reactions of the right ventricle and were able to detect early impairment of left ventricular output when the pulmonary artery was compressed about 58 per cent.

Although sudden drastic reduction in the patency of the pulmonary vascular bed may occur clinically, as for example in massive pulmonary embolization, and give rise to rapid fatigue and progressive failure of the right ventricle, this condition does not appear to be identical with the circulatory derangement that follows long-standing chronic pulmonary disease. In the latter condition right heart failure is probably a gradual summation effect of (a) mechanical overwork and (b) quantitative and qualitative alteration of coronary blood flow. As has been previously pointed out, the long-standing progressively increasing pulmonary resistance leads to a work-hypertrophy of the right ventricle. To maintain its nutrition this progressively enlarging myocardial mass requires a corresponding increase in its blood supply. The coronary circulation is relatively insufficient, quantitatively because of the unchanging and later even diminishing aortic pressures, and qualitatively because of the anoxemia. These factors lead to relative ischemia or anoxemia of the hypertrophying right ventricular myocardium, which in the presence of continued overwork of the right ventricle must eventually lead to its nutritional impairment and to consequent diminution of its functional capacity. It is highly improbable that in these

chronic pulmonary cases, the reduction in the patency of the pulmonary vascular bed ever approaches the critical value that was obtained in the above mentioned acute experiments.

SUMMARY

1. Circulatory measurements were employed in the study of pulmonary and myocardial insufficiency in chronic lung disease. The measurements employed were initial venous pressure, the rise of venous pressure during right upper abdominal quadrant compression, the arm-to-lung time (ether), the arm-to-tongue time (saccharin or decholin), and the lung-to-tongue time (saccharin time minus ether time).

2. Uncomplicated pulmonary insufficiency, as is commonly observed in emphysema, is usually attended by normal circulatory measurements, even when associated with right ventricular enlargement.

3. The presence of abnormal circulatory measurements indicates that pulmonary insufficiency is complicated by myocardial failure.

4. The myocardial failure accompanying pulmonary insufficiency is due primarily either to disease of the lungs giving rise to incipient or frank isolated right heart failure, or to unrelated coexisting cardiovascular disorders which result in either left ventricular or universal heart failure.

5. Incipient isolated right heart failure is characterized by the presence of a normal initial venous pressure, and a varying rise in this pressure during right upper quadrant compression. The arm-to-lung time may or may not be prolonged, and the lung-to-tongue time is normal.

6. Frank isolated right heart failure is characterized by high initial venous pressure, considerable rise on right upper quadrant compression, prolongation of the arm-to-lung time and a relatively normal lung-to-tongue time. This indicates that the slowing of the blood flow is confined to the right heart unit, that is, to the segment between the peripheral veins and the pulmonary arterial capillaries.

7. Left heart failure, which may occur as an incidental complication of pulmonary insufficiency, is characterized by normal initial venous pressure with or without a rise on right upper quadrant compression, a normal or slightly prolonged arm-to-lung time, and a considerably prolonged lung-to-tongue time. This indicates that the slowing of the blood flow is largely limited to the left heart unit, that is, to the segment between the pulmonary venous capillaries and the capillaries of the tongue.

8. Universal heart failure, secondary to disease of the left side of the heart and possibly also to coexisting pulmonary disease, is characterized by high initial venous pressure, with a considerable rise in right upper quadrant compression, prolongation of the arm-to-lung time and of the lung-to-tongue time.

9. Bronchial asthma with a few exceptions is characterized by normal initial venous pressure, absence of a rise of right upper quadrant pressure, normal or fast normal circulation times.

10. Cardiac asthma is differentiated from bronchial asthma by the presence of abnormal circulatory measurements, notably by the rise of venous pressure on right upper quadrant compression and by the prolongation of the lung-to-tongue time.

11. That incipient right heart failure also frequently accompanies left ventricular failure may be demonstrated by the method of compressing the right upper quadrant of the abdomen and observing the presence of a rise in the normal initial venous pressure level.

12. In chronic bronchopulmonary disease there is apparently no parallelism between the severity of the clinical symptoms and the slowing of the pulmonary blood flow. Even in those patients who, in addition, present the picture of isolated right heart failure, the clinical symptoms appear out of proportion to the degree of retardation of the circulation through the lungs.

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TRANSIENT AURICULAR FIBRILLATION AS A TOXIC MANIFESTATION OF DIGITALIS*

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WHILE auricular fibrillation is a common finding in patients with cardiac disease and failure and while digitalis is considered a sheet-anchor in the treatment of such patients, it is uncertain whether or not digitalis in therapeutic doses may bring about auricular fibrillation in patients whose cardiac mechanism was previously normal. A review of the literature reveals that there is no consensus of opinion in this regard and that most authorities do not consider that digitalis may produce auricular fibrillation. Cushny[1] stated: "Auricular fibrillation is said to have occurred under digitalis in cases of previously regular rhythm; in most, perhaps in all, of these cases, careful examination shows that the regular ventricular rhythm is accompanied by auricular flutter; it is not certain that auricular fibrillation is induced by digitalis unless flutter is present before the treatment is initiated." The same author, nevertheless, did produce auricular fibrillation in mammals in the third stage of digitalis action after very large quantities of this drug were injected. Cowan and Ritchie[2] and Lewis[3] in their recent textbooks on heart disease did not mention the possibility that digitalis may produce auricular fibrillation in patients. Robinson[4] studied a case of paroxysmal auricular fibrillation but was unable to draw any definite conclusion as to the influence of the drug on the persistence of the fibrillation. Luten[5] in his clinical studies of digitalis did not encounter auricular fibrillation as a toxic manifestation from his massive doses of digitalis. In a report on transient and recurrent auricular fibrillation, Patterson[6] was unable to show that digitalis was the cause of auricular fibrillation in any of his cases. Cookson[7] and Friedlander and Levine[8] studied the etiology of auricular fibrillation but did not mention the possibility of its precipitation by digitalis.

On the other hand, that digitalis may be responsible for attacks of auricular fibrillation has been suspected by a number of observers. As early as 1910, Mackenzie[9] described a case in a woman with rheumatic heart disease in whom auricular fibrillation appeared with slow ventricular rate at the height of digitalis effect and disappeared four days after the drug was discontinued. Danielopolu[10] reported three cases in which auricular fibrillation followed the administration of digitalis, in each instance the onset of fibrillation occurring coincidently with the maximum digitalis effect. Neuhoff[11] reported a boy with rheu-

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matic heart disease, in whom auricular fibrillation repeatedly appeared at the height of the effect of digitalis; when the drug was discontinued, fibrillation stopped at the end of a day or so. Reid[12] reported two cases, one of hypertensive and the other of syphilitic heart disease, in which partial heart-block and then auricular fibrillation developed after large doses of digitalis. Resnik[13] was perhaps the first who showed definitely that transient auricular fibrillation may follow digitalis therapy. He reported seven patients, five of whom had syphilitic heart disease, in whom digitalization produced auricular fibrillation; in all of these the abnormal rhythm disappeared in from one to six days after the discontinuance of the drug. Resnik advanced the following criteria as the basis for judging whether a causal relationship exists between the onset of auricular fibrillation and digitalis therapy:

1. Absence of history of previous attacks of auricular fibrillation.
2. Normal rhythm before administration of digitalis.
3. Appearance of auricular fibrillation after a dose of digitalis shown by clinical and electrocardiographic evidence to be an effective amount.
4. Persistence of abnormal rhythm as long as digitalis is continued in doses sufficiently large to compensate for the elimination of the drug.
5. Reestablishment of normal rhythm after discontinuance of digitalis.
6. Confirmation of the changes in rhythm by means of electrocardiographic records.
7. Exclusion of other factors which tend to bring on transient auricular fibrillation.

Schwartz and his associates[14] reported on three occasions a total of five cases in children with rheumatic heart disease and heart failure in whom transient auricular fibrillation together with other evidences of digitalis effect in electrocardiograms occurred when digitalis was administered in excessive doses. White[15] stated that, if given in excessive dosage, digitalis may produce auricular fibrillation. McMillan and Bellet[16] reported two cases of hypertensive cardiovascular disease in which auricular flutter was apparently produced by large doses of digitalis. In one of these cases, ventricular tachycardia set in after the onset of auricular flutter, and death soon followed. McEachern and Baker[17] in a study of the etiological factors of auricular fibrillation expressed the belief that in certain instances this rhythm is produced by excessive doses of digitalis. Their study included the five cases previously reported by Resnik and four additional cases, all in patients with syphilitic heart disease. They also referred to a personal communication from Brams and Gaberman, who studied the effect of large doses of digitalis on the electrocardiogram in nine subjects without heart disease and encountered transient auricular fibrillation in one instance (this was not mentioned in the article by Brams and Gaberman[18]).

The author has been impressed by the appearance of auricular fibrillation in patients with heart disease in association with full or excessive digitalization and by its disappearance in these cases on the withdrawal of the drug. In every one of the following 15 cases, all the criteria laid down by Resnik to establish the relationship between the onset of auricular fibrillation and digitalis therapy are met, with the exception of the fourth point, which has been neglected, since it seems unjustifiable to continue digitalis further when auricular fibrillation with slow ventricular rate and frequent ventricular extrasystoles make their appearance. Several cases have been excluded because the relations were not sufficiently clear, or because no electrocardiogram was secured during the attack of abnormal rhythm.

The digitalis used was of standard potency. Assayed on two series of cats on two occasions by Dr. C. Li, of the Department of Pharmacology,* it gave a potency of approximately 120 per cent in terms of cat units. The apparent lethal doses per kilogram of cat were respectively 0.083 ± 0.0028 gm. and 0.081 ± 0.0012 gm.

CASE REPORTS

CASE 1.—A Chinese housewife, aged twenty-seven years, was admitted to the hospital April 27, 1923, for symptoms of congestive heart failure of forty days' duration. Examination revealed cardiac enlargement, mitral stenosis, and congestive heart failure. The cardiac rhythm was regular. The patient was given 1.5 grams of digitalis in two days. On April 30, when the clinical condition improved, the heart rhythm became entirely irregular, and an electrocardiogram revealed auricular fibrillation, flat T-wave in Lead I, inverted T-wave in Leads II and III, and an irregular ventricular rate of about 70 per minute. Digitalis was discontinued. On May 2 an electrocardiogram showed sino-auricular rhythm, P-R interval 0.24 sec., diphasic T_2 and inverted T_3. On July 5 examination revealed normal mechanism, P-R interval 0.20 sec., and upright T-wave in all leads.

In a patient with rheumatic heart disease, cardiac enlargement, mitral stenosis, and cardiac insufficiency, auricular fibrillation followed the exhibition of digitalis which produced definite clinical and electrocardiographic effects. Both auricular fibrillation and T-wave inversion disappeared on withholding the drug.

CASE 2.—A Chinese male, aged forty-four years, was admitted on three occasions in 1924 and 1925 for congestive heart failure. Blood pressure varied from 194 systolic and 148 diastolic to 224 systolic and 158 diastolic. Cardiac rhythm was regular on the first and at the beginning of second admission on Jan. 12, 1925, when the patient was given 1.7 gm. of digitalis folia in twenty-four hours. On January 14 he developed auricular fibrillation, with alternating ventricular premature beats, and nausea and vomiting. Digitalis was discontinued on January 14. The electrocardiogram on January 20 revealed normal mechanism, with frequent ventricular extrasystoles. Six additional records showed no return of the circus mechanism.

The administration of 1.7 gm. digitalis in twenty-four hours to a patient with hypertensive cardiovascular disease and cardiac failure caused the appearance of auricular fibrillation, with bigeminal ventricular extrasystoles. The circus rhythm reverted to a sinus rhythm six days after the discontinuance of digitalis.

*The author wishes to acknowledge his indebtedness to Dr. Li for his kind help.

CASE 3.—A Chinese military officer, aged fifty-two years, was first admitted March 1, 1923, for moderate congestive heart failure of short duration. He was found to have syphilis with aortitis and frank aortic insufficiency. The blood Wassermann reaction was strongly positive. Six further admissions took place.

The cardiac mechanism as revealed by repeated electrocardiograms was normal. There was a moderate left axis deviation.

On his last admission, July 13, 1925, owing to his critical condition, large doses of digitalis were given. On the day of admission he received 0.6 gm. of digitalis. The electrocardiogram the next day showed normal mechanism. Digitalis was continued until July 21, when a total of 2.1 gm. was taken in nine days. On that date the electrocardiogram revealed auricular fibrillation, inverted T in Lead I, and low T in Lead II. Digitalis was discontinued on July 23. The electrocardiogram taken July 24 still showed auricular fibrillation, while records on July 27 and August 3 showed sino-auricular rhythm with prolonged P-R interval.

In this patient with syphilis of the cardiovascular system the development of auricular fibrillation was apparently related to digitalis, and reduction in its dosage was followed by reversion to sino-auricular rhythm. The T-wave change and the prolonged auriculoventricular conduction after reversion to sino-auricular rhythm also indicate the effect of digitalis.

CASE 4.—A Chinese man, sixty-four years old, was admitted on Feb. 26, 1930, to the Surgical Service for regurgitation of food for eight months. The findings were essentially normal except for signs pointing to carcinoma of esophagus. The heart was normal; rhythm, regular; blood pressure, normal. There was no venous engorgement. The patient was first operated upon on March 14. On March 18 atelectasis of the left lung was noted, and the heart and the trachea were displaced to the left. The general condition was fair, but the respiratory rate increased to about 23 per minute. With a view to strengthening a displaced heart before the contemplated second operation, which was for excision of the epithelioma, three intramuscular injections of 3 c.c. each of digipuratum at three-hour intervals were given on March 18, and 0.1 gm. of digitalis folia by mouth every day from March 19. On March 19, when the equivalent of 1 gm. had been given, auricular fibrillation and occasional ventricular extrasystoles appeared. On March 21, when patient was receiving 0.1 gm. digitalis per day, the cardiac mechanism reverted to normal, but the T-waves were still flat. The patient died on the operating table March 22.

It appears that the intramuscular injection of 0.9 gm. of digitalis precipitated auricular fibrillation in an elderly man with carcinoma of esophagus but without apparent heart disease or heart failure.

CASE 5.—A Chinese policeman, aged forty-three years, was admitted June 17, 1930, for congestive heart failure for about one month. The history gave multiple venereal exposures in the past. The symptoms became rapidly worse after the onset. The heart was markedly enlarged to the left. There were widened retromanubrial dullness and frank signs of aortic incompetency. The rhythm was regular; edema marked. Both Wassermann and Kahn reactions of the blood were strongly positive.

On admission on June 17 the electrocardiogram revealed normal mechanism and left axis deviation. The patient was given 1.5 gm. of digitalis in twenty-four hours. On June 19 the electrocardiogram showed auricular fibrillation, a slow ventricular rate of about 53 per minute, and diphasic T-waves in all leads. Digitalis 0.2 gm. was given on that day, and 0.1 gm. on June 20; it was omitted from June 21 to 23. On June 24 the electrocardiogram revealed reversion to normal mechanism, low T-waves, and occasional ventricular extrasystoles. Auricular fibrillation recurred on July 31, when marked nausea and vomiting also appeared, after resumption of digitalis. This again disappeared eleven days after the second withdrawal of the drug.

In a patient with syphilis of the cardiovascular system and advanced cardiac failure, full digitalization produced no beneficial response, but apparently brought on auricular fibrillation which disappeared on reducing the dose of digitalis. Slow ventricular rate during auricular fibrillation, inversion of T-waves, and nausea and vomiting support the view that auricular fibrillation was a toxic manifestation of digitalis in this case.

CASE 6.—A Chinese man, aged forty-nine years, was admitted July 15, 1931, for congestive failure for six months. The rhythm was regular, blood pressure, 158/124.

The patient was taking digitalis before admission, when the electrocardiogram showed partial auriculoventricular heart-block (P-R interval 0.24 sec.) and left axis deviation. After admission no digitalis was given for five days. From July 20 to July 27, 1.4 gm. of digitalis were given. On July 28 auricular fibrillation was detected clinically and confirmed by electrocardiogram.

Digitalis was not discontinued, but 0.1 gm. was ordered daily from July 28 to July 31. The electrocardiogram on July 31 revealed transient bigeminal rhythm owing to frequent occurrence of ventricular premature beats, in addition to auricular fibrillation. On August 3, there was auricular fibrillation with bigeminal ventricular extrasystoles. Digitalis discontinued from August 1 to 9. On August 10 the cardiac rhythm was regular again, and a record showed normal mechanism. Owing to the persistence of congestive failure, digitalis was resumed, with 1.7 gm. from August 10 to 20, and 0.1 gm. was given daily from August 12 to 20. The patient developed auricular fibrillation on or about August 19, when the electrocardiogram revealed auricular fibrillation, slow ventricular rate, and bigeminal ventricular premature beats. The patient coughed up fresh blood from August 17 until his death on August 20.

The occurrence of auricular fibrillation, a slow ventricular action, and bigeminal ventricular extrasystoles at a time when one expects a maximum digitalis effect, and their disappearance on withholding this drug, constitute evidence in favor of the view that digitalis caused auricular fibrillation in this patient.

CASE 7.—A Chinese man, aged forty years, was admitted April 28, 1933, for congestive heart failure for two months. He was critically ill, with pulse thready. There was massive effusion in the left pleural cavity with displacement of mediastinum, including the heart, to the right. The liver was enlarged below the costal margin. Three thoracenteses on the day of admission resulted in the removal of 13,100 c.c. greenish yellow pus.

The heart rhythm was regular on admission, when 6 c.c. of digipuratum was administered intramuscularly. On the next day, April 29, 0.6 gm. of digitalis by mouth and 2 c.c. of digipuratum intramuscularly were given in the morning. In the afternoon the ventricular rate suddenly dropped to about 40 per minute, with bigeminal rhythm. The heart rhythm was totally irregular after 5 P.M. An electrocardiogram taken at 8 P.M. on the same day revealed auricular fibrillation, complete auriculoventricular dissociation, bigeminal ventricular premature contractions, and left axis deviation. A second record on May 1 revealed a similar mechanism. Owing to the striking changes in the cardiac mechanism after digitalization, no digitalis was given from April 30 until July 17. Patient's circulatory condition improved gradually. He was discharged in good condition on July 19.

Subsequent records were interesting. On May 2 auricular fibrillation was still present, but not complete auriculoventricular dissociation. There were frequent ventricular extrasystoles of various shapes in Lead II. On May 15, when digitalis had been discontinued for fifteen days, the electrocardiogram first showed reversion to normal mechanism with P-R interval of 0.21 sec.

There is no doubt that in this subject, who suffered from massive pneumococcus pleurisy and whose heart was probably normal, digitalis (1.4 gm. in twenty-four

hours) produced auricular fibrillation, complete auriculoventricular dissociation and bigeminal ventricular extrasystoles. The T-wave inversion also indicates digitalis effect. All these changes disappeared in two weeks as digitalis effect passed off.

CASE 8.—A Chinese man, aged fifty-nine years, was admitted Jan. 12, 1934, for congestive heart failure for about one month. He had been entirely well previously. The patient was orthopneic with marked edema. There were typical central and peripheral signs of aortic insufficiency. The teleradiogram showed a widened aortic arch.

Digitalis 1.2 gm. was given on January 12-13.

An electrocardiogram taken January 13, after 0.6 gm. of digitalis on the day previous and 0.2 gm. on that morning, revealed normal mechanism and left axis deviation. Occasional extrasystoles noted on that day. On January 14 auricular fibrillation with T-wave changes and frequent ventricular extrasystoles appeared. Digitalis was omitted on January 14. From January 15 to 25 the patient received 0.6 gm. of digitalis. After this increase in dosage, the patient developed bigeminal rhythm in addition to auricular fibrillation (confirmed by electrocardiogram). Nausea and vomiting developed January 28.

Digitalis stopped from January 26. On January 30, normal mechanism was restored. Further observations showed that with smaller doses of digitalis, the patient never again developed circus mechanism (last electrocardiogram April 19, 1934).

In a patient with syphilis of the cardiovascular system, digitalis caused the appearance of auricular fibrillation, with bigeminal ventricular extrasystoles, and nausea and vomiting. Sino-auricular rhythm was restored upon reduction of digitalis.

CASE 9.—Patient, a Chinese housewife, aged thirty-four years, was admitted June 28, 1934, for pregnancy near term (para iv) and dyspnea, orthopnea, and cough for one month, and edema of legs for two days. Patient was obese, orthopneic, and cyanotic. The heart was enlarged to left; no murmur; gallop rhythm; blood pressure, 166/120. The abdomen was distended with the gravid uterus.

The electrocardiogram on June 29, the day after admission, revealed normal mechanism, upright T-waves in Leads I and II and inverted T-waves in Lead III. Digitalis medication was begun on June 29, when the patient received 0.8 gm. in divided doses by mouth, 0.7 gm. being given from June 30 to July 2. The electrocardiogram on July 2, after a total of 1.5 gm. in three days, showed still a normal mechanism, low T in Lead I, and diphasic T in Leads II and III. One and two-tenths grams of digitalis were administered from July 3 to 8. Labor started spontaneously on July 6, when delivery by breech presentation occurred. The patient's condition improved after admission, but nausea and vomiting began July 9, when heart rhythm was noted to be totally irregular. Digitalis was omitted on that day, and a record revealed auricular fibrillation, with all T-waves diphasic and the R-T interval deeper than before.

From July 10 on, digitalis therapy was relaxed, only 0.1 gm. per day being given until discharge on August 17. On July 12 the heart rhythm was regular, and a record revealed normal mechanism, auriculoventricular conduction at upper limit of normal (0.20 sec.), and diphasic T-waves in Leads I and II. The patient was last seen on April 20, 1935. The rhythm was always regular in later examinations.

In a patient who had hypertensive disease and cardiac failure precipitated by pregnancy and labor, 2.7 gm. of digitalis in ten days caused marked digitalis effect, as manifested by vomiting and transient auricular fibrillation.

CASE 10.—A Chinese merchant, male, thirty-seven years old, was admitted July 17, 1934, for shortness of breath for two years, cough and swelling of legs and of abdomen for six months. Examination revealed advanced congestive heart failure. The blood pressure was 166/130. The electrocardiogram, July 18, revealed normal

mechanism, low to flat T-waves, and left axis deviation. The patient improved after bed rest and digitalis, and he was discharged on August 3.

After discharge, the patient visited Cardiac Clinic frequently. He took 0.1 gm. digitalis daily from August 3 to 17. From August 18 to 30 he received a total dose of 2.1 gm. of digitalis in twelve days. When seen on September 1, he was very ill. He took 1.2 gm. of digitalis from September 1 to 8, when the patient returned without improvement, and the heart rhythm was noted to be totally irregular. He was readmitted September 9, when the electrocardiogram revealed auricular fibrillation with bigeminal ventricular extrasystoles and flat T-waves. After admission, the patient received no digitalis for six days, and cardiac rhythm returned to normal on September 15. Subsequent administration of digitalis was more cautiously undertaken, with no recurrence of auricular fibrillation.

A patient with hypertensive cardiovascular disease developed auricular fibrillation, with bigeminal ventricular premature contractions, after 3.2 gm. of digitalis in twenty days. Omission of digitalis for six days was followed by return to normal mechanism.

CASE 11.—A young girl, aged fourteen years, was admitted Sept. 27, 1934, for palpitation of heart and dyspnea for several months. The symptoms were suggestive of intermittent claudication of left leg for three months one year ago. She was underdeveloped and undernourished. The heart was enlarged to the right and to the left upper, with findings suggestive of a mitral lesion. No roentgenological evidence of coarctation of aorta was noted. Right brachial arterial pressure varied between 140-170 systolic and 80-98 diastolic. Arterial pulsations were absent in the left arm, over abdominal aorta, and in the lower extremities. The liver was enlarged.

The patient received no medication from admission to October 14. The electrocardiogram on September 20 revealed normal mechanism, tendency to left axis deviation, and upright T-waves. Because of increase of congestive heart failure, the patient was given digitalis in the amount of 3.9 gm. in a period of forty-two days from October 15 to November 26. On November 10 the electrocardiogram showed normal mechanism and a definite lowering of T in all leads.

The digitalis dosage was increased on November 28, as the patient showed no response to treatment. Digitalis 0.8 gm. was given from November 28 to 30. On December 1 the patient developed for the first time nausea and vomiting and, in the afternoon, a "very irregular" heart rhythm for a few hours—no electrocardiogram. From December 1 to 10 digitalis 0.1 gm. was given daily. On December 8 and 10 marked nausea and vomiting were present. Examination showed a totally irregular rhythm, and digitalis was stopped from that date. The electrocardiogram revealed auricular fibrillation, diphasic T in Leads I and II and inverted T in Lead III. The circus rhythm lasted about thirty-one hours. The record on December 12 revealed normal mechanism, but T-wave changes persisted. The patient was discharged improved on December 17. Four days later patient was readmitted in a critical condition. She died with regular sinus rhythm on December 22.

A young girl who had coarctation of aorta and questionable rheumatic heart disease and who was small in stature (height 137 cm. and weight 26 kg.) was probably given somewhat too much digitalis, chiefly on account of her lack of favorable response to the drug. Digitalis seems to have caused transient auricular fibrillation, which disappeared about thirty-one hours after the withdrawal of the drug. Other electrocardiographic signs of digitalis effect were seen.

CASE 12.—A Chinese male, aged fifty years, was admitted Nov. 28, 1934, for congestive heart failure for two months. There were hydrothorax and ascites. The heart was markedly enlarged to the left and there were central and peripheral signs of frank aortic regurgitation.

The electrocardiogram on the day of admission showed normal mechanism, upright T in Leads I and II, and diphasic T in Lead III. Digitalis 1.3 gm. was given from November 28 to 30. Patient became nauseated on November 30, when cardiac rhythm was found totally irregular and a record revealed auricular fibrillation, depressed R-T in Lead II, and inverted T in Lead III. Digitalis was discontinued from November 30 to December 5. The electrocardiogram on December 4 revealed normal mechanism, P-R interval of 0.20 sec., but the R-T interval was still depressed in Lead II and the T-wave inverted in Lead III.

Nausea and auricular fibrillation developed in a patient with syphilitic heart disease after 1.3 gm. of digitalis in two days. Reduction of the dosage resulted in the disappearance of circus mechanism in four days.

CASE 13.—A Chinese housewife, aged forty years, was first seen in the out-patient clinic Oct. 18, 1928, when she had had moderate congestive heart failure for three months. Examination showed mitral stenosis and a regular rhythm. The electrocardiogram before digitalis showed normal mechanism, right axis deviation, upright T in Leads I and II and inverted T in Lead III. The patient was treated successfully for six years in the Cardiac Clinic with digitalis and general measures. Sixteen electrocardiograms during this six-year period all showed normal mechanism. The patient's condition became worse on Nov. 20, 1934, when she was admitted to the hospital. By that day she had received 1.3 gm. of digitalis in seven days. After admission another gram of digitalis was given, a total of 2.3 gm. from November 13 to 24. There was no vomiting prior to admission, but from November 20 on, there were both nausea and vomiting. Auricular fibrillation developed on November 24. The electrocardiogram showed coarse circus waves, a ventricular rate of about 65 per minute, and flat T in Lead I and inverted T in Leads II and III. Digitalis was immediately stopped. Two days later normal mechanism returned, with occasional ventricular extrasystoles. The patient gradually developed uremia and was discharged against advice on November 28. The cardiac rhythm remained regular to the time of discharge.

In a patient with rheumatic heart disease and chronic diffuse nephritis, 2.3 gm. of digitalis in twelve days caused the onset of auricular fibrillation, which reverted to normal mechanism two days after the discontinuance of digitalis.

CASE 14.—A Chinese housewife, aged forty years, was first admitted Feb. 12, 1935, near labor (para ii). A living baby was delivered on February 14. There were cough, shortness of breath, and edema of legs for three weeks. Examination showed cardiac enlargement, mitral stenosis, and moderate congestive failure. The rhythm was regular. The electrocardiogram on February 14 revealed normal mechanism. Digitalis 2.1 gm. was given from February 13 to 25. The general condition improved. Auricular fibrillation developed February 26, from which day digitalis was discontinued. Normal sinus rhythm was restored March 4.

In a woman in labor with rheumatic heart disease, digitalis therapy probably played a rôle in the postpartum production of auricular fibrillation, although it developed several days after the expected time of maximum digitalis effect.

CASE 15.*—A Chinese man, fifty-seven years old, was admitted twice, first, Jan. 23, 1934, and second, Jan. 26, 1935. On first admission the patient showed signs of moderate congestive heart failure which had been present for eight days. There was no evidence of valvular lesion. The blood pressure was normal. The patient improved after rest and digitalis. The electrocardiogram on Jan. 23, 1934, before digitalis, revealed normal mechanism and upright T-waves in all leads. After 1.9 gm. of digitalis in fourteen days, a second record showed flat T_1 and diphasic T_2 and T_3. By February 12 patient had received 2.4 gm. of digitalis in twenty-one

*This case is reported in detail in a separate communication by Dr. C. W. Rien and Dr. K. Y. Ch'in.

days. On that day clinical examination revealed a transient attack of totally irregular heart rhythm, presumably auricular fibrillation, but the irregularity had disappeared several hours later when the electrocardiogram was taken. Besides the T-wave changes similar to those of the second electrocardiogram there was also prolongation of the P-R interval to 0.24 sec.

During the interval between the first and second admissions, the patient visited the Cardiac Clinic regularly. On three or four occasions a low pitched rumbling diastolic murmur was heard at the apex. The patient was constantly under the effect of digitalis during this interval, when his cardiac rhythm was always regular.

The condition became worse in January, 1935, and the patient required admission on January 26. At that time he showed marked dyspnea and orthopnea. The heart was then markedly enlarged. Venous pressure was 250 mm. of blood by direct method.

Patient had received digitalis 11.6 gm. in 109 days up to the day of admission; he was given 0.5 gm. additional on January 26 and 27. He vomited a great deal from January 26 to 28. On January 28 the cardiac rhythm became totally irregular. Digitalis was discontinued for the next two days and an electrocardiogram was taken, which showed auricular fibrillation, flat T_1, and inverted T in Leads II and III. Because of persistence of congestive failure, digitalis was again administered, 0.5 gm. from January 30 to February 2. Nausea and vomiting increased. Digitalis was discontinued February 3. The electrocardiogram taken on February 4 revealed auricular fibrillation, frequent ventricular premature contractions, sometimes bigeminal in rhythm, and inverted T-waves.

After withdrawal of digitalis, the patient improved gradually. Nausea and vomiting subsided. Cardiac rhythm became regular from February 9. The electrocardiogram on February 13 revealed normal mechanism, sinus bradycardia, and right axis deviation. Cardiac rhythm remained regular until sudden death occurred on March 4, 1935.

Necropsy revealed a myxoma of left auricle protruding into and obstructing the mitral orifice, marked hypertrophy and dilatation of right ventricle, and extensive chronic passive congestion.

In an unusual case of primary myxoma of the heart with apparently normal endocardium and myocardium at autopsy, auricular fibrillation with bigeminal ventricular extrasystoles and other evidences of digitalis intoxication developed during the use of digitalis. On the eighth day after the discontinuance of the drug the mechanism became normal, and remained so until sudden death took place twenty-four days later.

DISCUSSION

A careful examination of the foregoing case records and of Table I will leave little doubt that the onset of auricular fibrillation was caused by large doses of digitalis. In Cases 4 and 7 there was no definite evidence of organic heart disease, and the patients suffered respectively from epithelioma of the esophagus and suppurative pneumococcal pleurisy. Digitalis was given in the first case with a view to supporting the circulation before a contemplated major surgical operation in an elderly individual, and in the second case on account of signs of circulatory failure due to marked displacement of the heart. Another case (No. 15) concerned a patient whose heart was normal except for a solitary myxoma of the left atrium, which led to mitral valvular obstruction and to hypertrophy and dilatation of the right side of the heart. In four cases there was frank syphilitic cardio-

vascular disease with aortitis and aortic insufficiency. In all cases the onset of auricular fibrillation was associated with other signs of digitalis effect, such as slow ventricular rate, T-wave inversion, bigeminal rhythm with ventricular premature contractions, and often nausea and vomiting. In all instances the mechanism reverted to normal after the withdrawal (in thirteen cases) or reduction (in two cases) of digitalis. A period of from two to fifteen days (average, five days) elapsed from the time of withdrawal of digitalis to reversion to sinus rhythm. This fairly long period for a marked digitalis effect to wear off is not surprising in view of the previous finding[19] that after moderate doses of digitalis given within a period of eight to twelve hours to a group of patients who were not previously under the influence of this drug, its effects were often still discernible in the electrocardiograms three or four weeks later.

TABLE I

SUMMARY OF FIFTEEN CASES OF AURICULAR FIBRILLATION PRODUCED BY DIGITALIS

CASE NO.	SEX	AGE	DIAGNOSIS	AMOUNT OF DIGITALIS RECEIVED AT ONSET OF AURICULAR FIBRILLATION (GM.)	NUMBER OF DAYS WITHOUT DIGITALIS BEFORE REVERSION TO NORMAL MECHANISM
1	F	27	Rheumatic, mitral stenosis	1.5 in 48 hr.	3
2	M	44	Hypertensive	1.7 in 24 hr.	6
3	M	52	Syphilitic, aortic incompetency	2.1 in 9 days	3
4	M	64	Epithelioma of esophagus, preoperative	1.0 in 24 hr. (0.9 intramuscular)	2 (Had 0.2 gm. during this period)
5	M	43	Syphilitic, aortic incompetency	1.5 in 24 hr.	3
6	M	49	Hypertensive	1.4 in 8 days (Had unknown amount of digitalis before admission)	9
7	M	40	Pneumococcus suppurative pleurisy	1.4 in 24 hr.	15
8	M	59	Syphilitic, aortic incompetency	1.2 in 24 hr.	4
9	F	34	Hypertensive; parturition	2.7 in 10 days	3 (Had 0.2 gm. during this period)
10	M	37	Hypertensive	3.2 in 20 days	6
11	F (Height 137 cm. Weight 26 kg.)	14	Congenital, coaretation of aorta	2.0 in 13 days	31 hr.
12	M	50	Syphilitic, aortic incompetency	1.3 in 48 hr.	4
13	F	40	Rheumatic, mitral stenosis	2.3 in 12 days	2
14	F	40	Rheumatic, mitral stenosis; parturition	2.1 in 12 days	6
15	M	57	Myxoma of heart	12.1 in 111 days	6

The mechanism of the production of auricular fibrillation by digitalis is not clear. Resnik[13] believed that the phenomenon was due in some cases to strong stimulation of the vagus nerves but that in most cases it was due to direct action upon the myocardium. In one of Resnik's cases there was a reversion to normal rhythm following the use of atropine. He also believed that myocardial failure was an important predisposing, though not a direct, cause of transient auricular fibrillation.

Lewis and his associates[20] showed that vagal stimulation reduced the absolute refractory period of the dog's auricular muscle beating at rates of about 200 per minute to from one-fifth to one-sixth of its full value. Although the refractory period and its variations in human beings are unknown, it is known that the electric systole (Q-T interval of the electrocardiogram) is shortened by digitalis, not only absolutely but in relation to the cardiac rate.[21] This change speaks for shortening of the refractory period which favors the persistence, if not the onset, of the circus mechanism.

It has been demonstrated by a number of observers that vagal stimulation tends to favor the development of auricular fibrillation.[22] This view had been recently substantiated by Nahum and Hoff,[23] who converted the normal mechanisms of four hyperthyroid patients and ten electrically stimulated cats into auricular fibrillation by the administration of acetyl-β-methylcholine chloride. It appears probable, therefore, that vagal stimulation plays an important rôle in the production of auricular fibrillation by digitalis.

As to the direct action of digitalis on the myocardium, it is difficult to state positively its rôle in the production of auricular fibrillation. Lewis[24] found that this direct action of digitalis slowed the conduction and prolonged the refractory period of the mammalian auricle. Cushny[25] showed that one of the main toxic effects of digitalis is to increase the irritability of the myocardium, leading to ectopic beats and to auricular fibrillation. It is possible, therefore, that the direct action of digitalis on the myocardium and its indirect action through the vagi may not oppose each other and that both may be responsible for the development of auricular fibrillation, especially in the presence of other factors which in themselves may excite the onset of circus mechanism, such as myocardial disease and cardiac failure.

It has already been pointed out[17] that the production of auricular fibrillation as a result of digitalization is not a matter of mere academic interest. Although, in general, auricular fibrillation with a rapid ventricular rate is an indication for digitalis, the onset of this rhythm in patients who have received large doses of digitalis constitutes an indication that a toxic effect of digitalis is present. It is possible that the further use of the drug might give rise to ventricular tachycardia

or fibrillation or even irreversible cardiac damage. It appears also true that discontinuance or marked reduction rather than further administration of digitalis gives the best chance for improvement in cardiac efficiency and for reversion to normal mechanism.

SUMMARY

In fifteen patients, two without and thirteen with heart disease and congestive failure, full digitalization caused the appearance of auricular fibrillation together with other signs of digitalis intoxication. The abnormal rhythm in all cases disappeared several days after the discontinuance of digitalis.

Under certain circumstances transient auricular fibrillation is a toxic effect of digitalis and its occurrence under these circumstances is an indication for the withdrawal of the drug.

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THE EFFECT OF STELLATE GANGLIONECTOMY ON THE CARDIAC FUNCTION OF INTACT DOGS

And Its Effect on the Extent of Myocardial Infarction and on Cardiac Function Following Coronary Artery Occlusion*

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FOR SOME years stellate ganglionectomy was performed by a number of surgeons for the relief of pain in angina pectoris. Others doubted the value of the procedure and even condemned it heartily saying that it not only failed to relieve pain satisfactorily, but predisposed the heart to sudden failure and prevented a person with a diseased heart from receiving warning of overwork. In the last few years, however, several who were opponents of stellate ganglionectomy in cases of angina pectoris have changed their views on both clinical and experimental grounds. The following physiological and pathological experimental studies support the view that stellate ganglionectomy does not predispose a heart suffering from circulatory disturbances to failure but definitely minimizes the ill effects of such changes.[1-8]

LITERATURE

For present purposes a few of the many excellent clinical résumés of the literature bearing on the question at hand suitably summarize the pertinent facts and theories. It is notable that several early opponents of stellate ganglionectomy as an operative treatment for angina pectoris have changed their views considerably in recent years. Danielopolu, on clinical grounds, and Leriche, on both clinical and experimental grounds, were among those who some years ago felt that motor sympathetic fibers essential to the heart passed through the stellate ganglia, and that their removal was contraindicated because sudden asystole might be precipitated, or the function of the heart might be definitely limited. Cutler, who summarized the literature excellently on several occasions, did not omit to mention Danielopolu's warnings; though he himself adjudged the procedure noninjurious to dogs and beneficial to persons suffering from angina pectoris. More recently Leriche has by both clinical and experimental work found occasion to reverse his previous judgment and feels that stellate ganglionectomy is distinctly beneficial in cases of angina pectoris since the procedure lessens the extent of infarction following coronary closure and offsets any tendency to ventricular fibrillation. Swetlow apparently found injection of the ganglia, from the level of C8 to T7, capable of relieving the pain of angina in many cases and quite harmless.[1-6, 9-12]

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The exact scientific explanation for these various clinical opinions is marred by disagreement regarding the paths and positions of the cell stations of the nerves supplying the heart, and the functions of these nerves. Excellent physiological studies, however, have shown that stellate ganglionectomy has no effect on the cardiac function of dogs and their ability to work. It has been found experimentally that the surface temperature of an infarcted area of heart muscle does not change with removal of the stellate ganglia and stimulation of the sympathetic fibers to the heart produces no rise in temperature. It seems proved that, though motor, cardiotonic, vasodilatory, and sensory fibers concerned in the reflex reactions of the heart are generally supposed in dogs to pass to and from the heart by way of the stellate ganglia, the removal of these structures is without deleterious effect. Such a conclusion is supported by the fact that various chemical and hormonal influences may adequately replace the nervous reflexes of the heart in its various reactions to general bodily activity.[13, 14, 15]

The anatomical data most acceptable as a background for the above findings are briefly as follows: Sensory fibers to do with pain leave the heart in the human by the middle and inferior cardiac nerves, travel caudally from the middle and inferior cervical ganglia to the stellate ganglia and reach the cord by way of white rami from the sympathetic chains, from the level of C7, C8, or T1 to T4, or sometimes further caudad still. In dogs the pain fibers run to the stellate ganglia and to a varying number of the upper thoracic ganglia. Stellate ganglionectomy largely interferes with such fibers. Other sensory fibers, more important to heart function than these, and concerned in three well-known reflex arcs, are, however, left quite intact when the stellate ganglia are removed. The depressor nerves from the region of the aortic arch for the regulation of blood pressure and pulse, the fibers from the venous side of the heart which form the sensory side of the Bainbridge reflex and have to do with the regulation of cardiac filling and pulse rate, and the carotid sinus reflex sensory fibers regulating heart rate do not pass through the stellate or upper thoracic ganglia. Except for some sympathetic efferent fibers of the Bainbridge reflex which pass through the stellate ganglia to the heart, the efferent fibers of these important reflex arcs are also unharmed by stellate ganglionectomy in both human and dog, for the majority of the efferent fibers are carried in the vagus nerves.

The efferent sympathetic cardiac fibers in man arise in the lateral horns of the gray matter in the upper thoracic cord and pass to the heart from the superior, middle and inferior stellate, and several of the upper thoracic ganglia. In the dog they all pass from the stellate ganglia to the heart. It is over such fibers that much disagreement occurs, for they have been credited with quite various morphologies and functions from time to time. At present they are considered as accelerator and tonic

to the heart and as vasodilatory to its vessels. As mentioned above, chemical substances, notably adrenalin, appear capable of replacing efficiently the functions of these fibers so that their loss is theoretically unimportant.[12, 13, 15-18]

METHOD

Leriche tied off various parts of the coronary circulation in dogs that had had, and also in those that had not had, stellate ganglionectomy performed. He examined the hearts at various intervals afterward and, where comparable amounts of coronary supply had been tied off, reported that the smallest amount of infarction was found in the dogs that had had stellate ganglionectomy done the longest time before the ligation. Cannon and others have studied the pulse, respirations, and work ability of exercising dogs and found that stellate ganglionectomy had no effect on these measures of cardiac function. We therefore combined these methods, adding a study of basal and exercise cardiac output since it was found that a fairly delicate test of this function could be made.

It is true that many cases of angina pectoris in the human present no definite obstruction of the coronary arteries at autopsy, that the exact nature of angina pectoris in the human is unknown, and that ligation of coronary vessels does not necessarily parallel the conditions extant in the patient suffering from angina pectoris. But, as pathological studies become more searching, more and more hearts of patients who suffered from angina are found to bear evidence of coronary occlusive changes, and increasing numbers of reports are seen of angina cases which were found during life or at autopsy to have been in reality cases of coronary thrombosis. Further, it is commonly felt nowadays that angina pectoris is due to anoxemic changes in the myocardium in the final analysis. It seemed reasonable, in consideration of these points, to proceed as detailed below.[4-6, 15, 19-26]

Male dogs of as similar size and temperament as possible were trained to run on a treadmill, to cooperate in studies of pulse, respiration, blood pressure, and basal and exercising cardiac output. Five of these dogs, after such studies and under proper anesthesia, had the stellate ganglia along with two to four of the upper thoracic ganglia removed. The previous tests were then rechecked, and, when stable readings were reached, the anterior descending branch of the left coronary artery was tied at about its midpoint. This usually gave an area of epicardial blueness about 1½ inches in diameter, an area approximately one-quarter of the area of the left ventricle. If the area first tied was not quite large enough, ligatures were placed more proximally on the vessels to give the desired extent of infarction. As hearts in dogs of similar size varied in their measurements somewhat, and as the coronary vessels deviated considerably in their mode of distribution and extent of anastomosis, it was not always possible to be sure that exactly similar areas of heart muscle had been infarcted. Such variations were carefully noted and suitable allowances made. At operation, measurements of the size of the heart and of the area of infarction were taken. When the dog was entirely recovered (and usually in forty-eight hours no evidence of ill effect was present) resting and exercise readings were again taken until it was evident that stable readings were being obtained.

TABLE I

TABULATION OF THE VARIOUS TESTS ON DOG 3. NEITHER STELLATE GANGLIONECTOMY NOR, LATER, CORONARY LIGATION MADE AN APPRECIABLE CHANGE IN THE TESTS

DOG NO.	WT. KG.	PULSE RECOVERY			B. P.		RESP'RATIONS RECOVERY			O_2 CONSUMPTION C.C./MIN.		BLOOD O_2 ART. VEN.	BLOOD O_2 ART. VEN.	ART. VEN. O_2 DIFFERENCE		ART. O_2 C. P.	CARDIAC OUTPUT		E. C. G.	HEART SIZE
		REST	WORK	TIME	REST	WORK	REST	WORK	TIME	REST	WORK	REST	WORK	REST	WORK		REST	WORK		
3	13	100	180	4′	90-140		20	50	3′	112.0		17.9-12.1		5.8		19.3	1931			
					85-140					95.6		14.6- 9.1		5.5			1738		Feb. 1	Mar. 29
										113.3		17.5- 9.2		8.3		23.7	1365			
										110.8		17.8-11.7		6.1		21.4	1816			8.5
	12																			
						105-160					373.5		16.1-11.2		4.9			7622		
						100-170					497.5		14.5-10.8		3.7			13446		
											462.3		14.1-11.2		2.9			15941		
		Stellate Ganglionectomy April 4, 1933																		
										108.5		14.0- 8.6		5.4			2009			
	12.7	70	150	6′	78-130		20	60	3′	183.8		19.9-12.5		7.4		20.2	2485		April 7	May
					80-135					152.9		16.2-11.6		4.6			3323			
	12.2	100	180	6′						126.6		16.2-10.1		6.1			2078			8.5
						100-165					563.5		15.3- 9.3		6.0			9391		
						105-175					664.6		18.0-12.0		6.0			11076		
											324.9		19.6-15.7		3.9			8330		
											579.0		16.4-12.5		3.9			14846		
		Coronary Ligature May 23, 1933																		
										82.7		16.8-12.2		4.6			1797			May 23
	12.2	90	160	5′	100-130		20	60	4′	129.5		15.0-10.7		4.3		19.6	3001			May 24
					90-140					73.9		15.3-12.9		2.4			3079			May 25
										149.5		16.9-10.9		6.0			2491			May 28
										131.0		16.8-11.5		5.3		22.8	2452			Aug. 15
										128.4		18.4-11.5		6.9			1860			
																				8.5
						110-160					433.0		12.9-10.2		2.7			16037		
						108-170					391.0		18.4-15.5		2.9			13482		
											583.7		16.3-12.4		3.9			14948		

Another five of the dogs, following the usual tests, were subjected to as exactly similar coronary occlusion as possible, no stellate ganglionectomy being done first. When the dogs had sufficiently recovered, the tests were repeated until stable results were obtained.

Ten other dogs that had no cardiac output estimations done were used to test the mortality and morbidity between dogs subjected to coronary closure after stellate ganglionectomy and dogs subjected to similar coronary closure without previous ganglionectomy. These dogs were divided into two groups of five dogs each. The ligature in each case was placed quite close to the origin of the anterior descending branch of the left coronary artery, giving an area of infarction considerably greater than one-quarter of the left ventricle.

The dogs were sacrificed only after many check studies had been done. They were usually observed from four to six months after the last operation. Great care was taken throughout to see that all tests were done as uniformly as possible. The hearts were finally preserved for microscopic study to check the gross measurements of the area of infarction.

Electrocardiograms were taken on many dogs before and after the various procedures, especially after coronary ligature was done, to confirm the presence of infarction.*

The method is summarized in several typical protocols.

Stellate Ganglionectomy Prior to Coronary Ligature.—Dog 3, 1933, a male collie, weight 13 kg. (Table I).

January, February, March.—Dog trained readily for various tests; and pulse, respiration, blood pressure, basal and exercise cardiac output readings taken repeatedly until fairly level results were obtained. Electrocardiographic readings and heart size by x-ray examination were recorded.

April 3, 1933.—A bilateral stellate ganglionectomy was done through lateral chest wall incisions, three ganglia below each stellate being taken. The course after operation was uneventful. A bilateral Horner syndrome was present.

April, May.—Pulse, respiration, blood pressure, basal and exercise cardiac output studies were repeated until readings were stable. Electrocardiogram and the heart size were again recorded.

May 23, 1933.—The heart was exposed through a left rib-spreading incision. The left marginal artery, which was the first large branch of the left anterior descending ramus, was tied 1 cm. from its origin. An area of cyanosis 1 cm. in diameter developed just distal to the tie. There was a good anastomosis evident between the posterior artery of the left ventricle and branches of the anterior descending branch of the left coronary artery. Two ligatures were placed 2 cm. from the origin of the anterior descending branch of the left coronary artery. An area 2 cm. by 3 cm. turned blue, the area so affected extending from the septum in front to the left marginal artery, and from the region of the tie to the apex. The heart measured 7.5 cm. from apex to base. There was no change in cardiac function noted other than a lack of contractility in the part infarcted. The chest was closed, and there was an uneventful course after operation.

June, July, August, September.—All tests done before stellate ganglionectomy and coronary ligation were repeated. There was no evidence of cardiac embarrassment. There was no change in the size of the heart.

Oct. 10, 1933.—The dog was killed. The heart showed an area of infarction 4 cm. by 2 cm. by 0.5 cm., the greatest measurements being taken. There was marked

*We wish to thank Miss Elizabeth Lambert, of the Department of Physiology of the Harvard Medical School, for her generosity in making our electrocardiographic studies for us.

TABLE II

TABULATION OF THE VARIOUS TESTS ON DOG 247. NO STELLATE GANGLIONECTOMY WAS DONE PRIOR TO CORONARY LIGATION WHICH PERMANENTLY ELEVATED THE RESTING CARDIAC OUTPUT, AND LOWERED THE EXERCISE OUTPUT

DOG NO.	WT. KG.	PULSE RECOVERY			B. P.		RESPIRATIONS RECOVERY			O_2 CONSUMPTION C.C./MIN.		BLOOD O_2 ART. VEN.		ART. VEN. O_2 DIFFERENCE		ART. O_2 C. P.	CARDIAC OUTPUT		E. C. G.	HEART SIZE
		REST	WORK	TIME	REST	WORK	REST	WORK	TIME	REST	WORK	REST	WORK	REST	WORK		REST	WORK		
247	19	100	180	4-7′	80-150		25	60	7′	147		22.0-18.4		3.6			3972			
					75-140					141		23.6-17.1		6.5		24.5	2169		June 3	June 3
					75-145					118		23.5-16.7		6.8			1735			8.0
	17.6					98-170					330		18.3-13.4		4.9			6734		
						95-168					579		20.8-16.0		4.8	24		12020		
						98-170					434		17.3-13.4		3.9			11128		
		Coronary Ligature June 14, 1933																		
	15.8	95	160	4′	78-140		25	60	4′	157.3		20.5-16.2		4.3			3658			June 14
										184.0		19.0-13.9		5.1		22.8	3607			June 15
		90	150	4′	78-140					184.0		17.3-12.0		5.3			3471			8.0
											542		22.4-17.6		4.8			11291		July 15
											442		22.4-12.9		9.5			4652		8.0
											482		18.8-12.5		6.3			7650		
											482		18.1-12.9		5.2			9296		

scarring and thinning in the area involved. Microscopic examination confirmed the extent of the infarcted area and the amount of scarring (Fig. 1).

Coronary Ligation Without Previous Ganglionectomy.—Dog 247, 1933, a male terrier, weight 16 to 18 kg. (Table II).

May, June.—The dog trained readily and good readings were obtained for the various tests as noted above.

June 12, 1933.—The heart was exposed through a left rib-spreading incision, and the first branch of the left anterior descending ramus of the left coronary artery

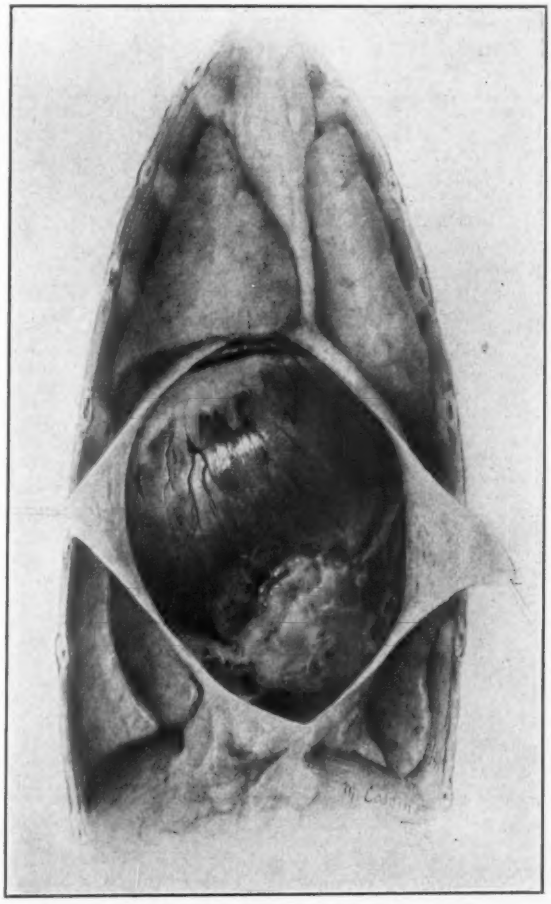

Fig. 1.—A drawing of the heart at autopsy of Dog 3. There was a fair degree of vascular proliferation about the infarct. The stellate ganglia had been removed prior to coronary ligation.

was tied at its origin. Only a small area of cyanosis developed. The ramus itself was now tied about 1 cm. distal to the left auricular tip. An area of cyanosis 2.5 by 1 cm. resulted. The heart measured 6 cm. from apex to base. No change in cardiac function occurred during the procedure other than lack of contractility in the infarcted area. The chest was closed in layers. The course after operation was uneventful.

July, August, September.—The pulse, respirations, and blood pressure were as before operation, but the resting cardiac output remained persistently high while

the exercise output was lowered in nearly every test. The size of the heart did not change.

Oct. 22, 1933.—The dog was sacrificed. An infarct 3 cm. wide was found extending from the apex toward the base of the heart for 5 cm. It was 1 cm. thick. There was marked scarring and thinning of the heart wall in the area of infarction (Fig. 2).

OBSERVATIONS

The data regarding pulse, respiration, and blood pressure in the groups with stellate ganglionectomy and without stellate ganglionectomy revealed no marked difference in reaction to coronary ligation either at

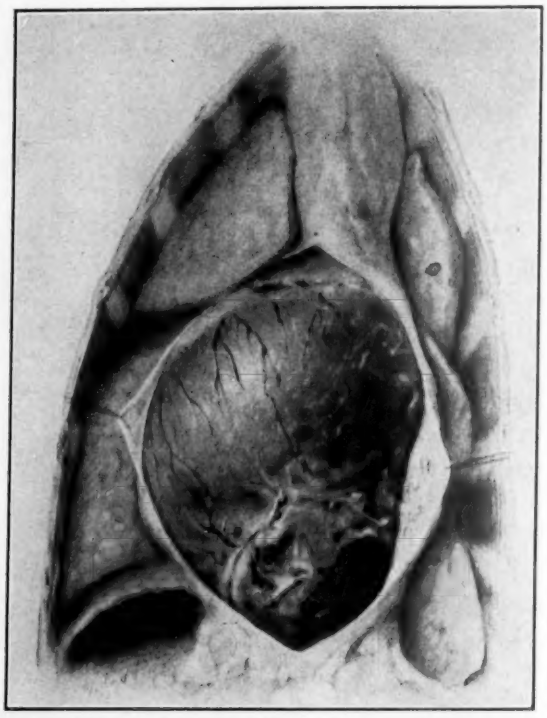

Fig. 2.—A drawing of the heart at autopsy of Dog 247. This dog did not have the stellate ganglia removed before coronary ligation. Some evidence of vascular proliferation was seen about the infarct, but vessels were much less prominent than about the infarct of Dog 3.

rest or during exercise. A very variable elevation of the resting pulse rate was observed in some of the dogs which had the coronary artery tied without previous ganglionectomy. Stellate ganglionectomy by itself produced no change in the resting or exercise readings.

In the ten dogs on which cardiac output estimations were done, a definite difference existed between the five that had stellate ganglionectomy performed prior to coronary ligation and the five that had only coronary ligation. The five dogs that had had no ganglionectomy gave resting cardiac output readings one and a half to twice as high after coronary

TABLE III

TABULATION OF THE VARIOUS TESTS ON DOG 60. NEITHER STELLATE GANGLIONECTOMY NOR, LATER, CORONARY LIGATION MADE AN APPRECIABLE CHANGE IN THE TESTS

DOG NO.	WT. KG.	PULSE RECOVERY REST	WORK	TIME	B. P. REST	WORK	RESPIRATIONS RECOVERY REST	WORK	TIME	O_2 CONSUMPTION C.C./MIN. REST	WORK	BLOOD O_2 ART. VEN. REST	ART. VEN. WORK	ART. VEN. O_2 DIFFERENCE REST	WORK	ART. O_2 C. P.	CARDIAC OUTPUT REST	WORK	E. C. G.	HEART SIZE
60/33	13	100	150	2′	85-135					199.58		19.45-15.36		4.1			5129		Dec.	March
		90	200	5′	90-120		16	28	2′	149.75		20.83-11.38		9.5		20.2	1584		7	7.5
					80-125		30	60	5′	113.21		19.52-12.64		6.9			1644			
						110-165					373.55		15.68-12.28		3.4	23.7		10389		April
						105-170					487.23		18.31-14.14		4.2			11600		7.5
	12.9					110-170					277.67		17.93-13.32		4.6	21.8		6031		
	Stellate Ganglionectomy																			
		80	150	6′	90-130															
					90-120		20	60	6′	164.0		22.9-16.4		6.5			2529		March	May
						105-165				108.0		16.5-13.1		3.5		24.6	3144		30	7.5
	15.2					103-170				185.3		22.1-16.3		5.8			3209			
										132.9		22.7-17.9		4.6		26.5	2769			
										116.0		18.2-11.9		6.3			1861			
											540.43		20.7-15.9		4.8			11259		
											490.8		18.2-14.8		3.4			14435		
	Coronary Ligature																			
		90	170	5′	90-120		30	60	5′	137.9		20.7-14.6		6.1			2259		June	May
					80-130					129.0		22.3-17.5		4.8		23.4	2666		3	7.5
						105-175				177.0		19.3-13.3		6.0			2932			June
	14.2					110-170				96.8		19.4-15.1		4.3		24.1	2211			7.5
										137.0		18.7-13.4		5.2			2596			Aug.
										162.0		21.1-14.3		6.7			2425			7.5
											437.0		19.5-13.4		6.1			7751		
											547.0		22.3-17.5		4.8			11396		
											402.0		22.7-19.1		3.6			11166		

TABLE IV

Tabulation of the Various Tests on Dog 220. No Stellate Ganglionectomy Was Done Prior to Coronary Ligation Which Permanently Elevated the Resting Cardiac Output

DOG NO.	WT. KG.	PULSE RECOVERY REST	WORK	TIME	B. P. REST	WORK	RESPIRATIONS RECOVERY REST	WORK	TIME	O_2 CONSUMPTION C.C./MIN. REST	WORK	BLOOD O_2 ART. VEN. REST	ART. VEN. WORK	ART. VEN. O_2 DIFFERENCE REST	WORK	ART. O_2 C. P.	CARDIAC OUTPUT REST	WORK	E. C. G.	HEART SIZE
220	15	60	160	4′	95-140		15	40	4′	186.9		20.0-13.9		6.1		24.2	3063		May	May 8
										184.9		23.0-15.8		7.2			2568		20	7.0
	14				90-135					265		22.0-15.7		6.3			4206		June	
						95-175										22.6			3	
											799		18.3-10.9		7.4			10798		
						105-170					725		18.7-12.2		6.5			11153		
	Coronary Ligature June 16, 1933																			
	13.6	90	170	4′	88-135		15	40	4′	222		18.8-14.5		4.3			5162			
					86-140					293		20.2-16.1		4.1		21.9	7146			June 16
						103-175				258		16.1-13.5		2.6			9923			7.0
						105-170					545		22.8-17.7		5.1			10698		July 18
											703		22.8-17.1		5.7			12333		7.0

ligation as before. This increase in resting output declined slightly in a few dogs after several months, but in the others persisted until autopsy four to five months following the operation of coronary ligature. One dog showed a marked decrease in the exercise output while the others showed no remarkable change in exercise output. The five dogs that had been subjected to stellate ganglionectomy showed no change in the cardiac output readings after this procedure, nor was there any change after the coronary ligation was done. These results are summarized in Table V. The figures given in the table for the resting and for the exercise cardiac outputs are not an average of the readings before or after the various procedures but were selected because they appeared to represent most accurately the true cardiac output reading for that particular series of tests from each group of readings. Tables I, II, III, and IV give very representative figures for the various tests on two dogs of each group.

TABLE V

Comparison between typical resting and exercise cardiac outputs, before (B) and after (A) coronary artery ligation, of 5 dogs with stellate ganglia intact, and 5 dogs with stellate ganglia removed

	DOGS WITH GANGLIA INTACT			DOGS WITH GANGLIA REMOVED		
		CARDIAC OUTPUT			CARDIAC OUTPUT	
	NO.	AT REST	AT WORK	NO.	AT REST	AT WORK
B	220	3051	11009	3	1818	13651
A		7164	13799		1872	15214
B	213	2825	14237	119	2810	18487
A		5096	14299		2640	15767
B	247	2169	11116	28	1593	11764
A		3645	7696		2122	11581
B	2	2207	12819	120	2322	13577
A		Fibrillation on ligation			2354	16095
B	260	2765	12803	60	1644	10899
A		Fibrillation on ligation			2259	11254

A comparison of the morbidity and mortality of the dogs which had stellate ganglionectomy done before coronary ligation with those that had only coronary ligation done revealed a striking difference. Ten dogs in all had ganglionectomy done before coronary ligation. They appeared to tolerate myocardial infarction well, only one dying soon after the procedure. The death was apparently due to ventricular fibrillation. The ten dogs, however, that had coronary ligature performed on them, without previous ganglionectomy being done, appeared to be more affected by the operation. Many of the dogs during the first few postoperative days displayed marked cardiac arrhythmia and much more general malaise than those dogs deprived of their stellate ganglia prior to coronary ligation. Moreover, two of the dogs died of ventricular fibrillation immediately after coronary ligation had been done and while

the heart was fully exposed. No accidental factors entered into these deaths, the operations being quite similar to all others done, and other conditions being quite unchanged. Three more dogs died quite suddenly and almost certainly of ventricular fibrillation within a few days of operation. Several of these deaths were witnessed by one of us and were remarkably similar to sudden death from cardiac failure in the human. Table VI summarizes these results.

TABLE VI

Comparison between the tolerance of 10 dogs with stellate ganglia intact, and 10 dogs with stellate ganglia removed, to coronary artery occlusion as evidenced by the incidence of acute cardiac failure following ligation

	DOGS WITH GANGLIA INTACT	DOGS WITH GANGLIA REMOVED
Acute cardiac deaths due to coronary ligation	260 337 213 2 342	320
Dogs healthy after coronary ligation	343 331 247 220 340	299 120 329 324 119 28 302 60 3

A study of the extent of the myocardial infarction in the various hearts following the operation of coronary ligation gave good evidence that ganglionectomy prior to coronary ligation favorably influenced the size of the infarct and its healing. Table VII lists the measurements of the infarcted areas of the various hearts at autopsy. By comparing the hearts from dogs with ganglionectomy prior to coronary ligation, to hearts of similar size from dogs without ganglionectomy prior to coronary ligation, it is seen that in the former the infarcts are invariably smaller. There appeared to be a more vigorous attempt at revascularization in and about the infarcts of the hearts of those dogs that had stellate ganglionectomy done prior to coronary ligation, but no clear-cut decision could be made on this point because of the great variations in the ordinary vascular supply of various hearts. In the group that had had ganglionectomy done prior to ligation, the first procedure had been carried out at various intervals before the second was done, but no definite indication of a difference in the extent of the myocardial infarction in this group of dogs was noted.

The electrocardiographic studies gave the usual evidence of infarction of heart muscle following coronary ligation.

TABLE VII

Comparison between the size of infarct at autopsy of 10 dogs with stellates intact and 10 dogs with stellates removed prior to coronary ligation

DOGS WITH STELLATES INTACT			DOGS WITH STELLATES REMOVED		
DOG	LENGTH OF HEART* (CM.)	SIZE OF INFARCT† (CM.)	DOG	LENGTH OF HEART (CM.)	SIZE OF INFARCT (CM.)
247	6.0	5.5 long 2.5 × 3.0 × 2.0 wide 0.5 × 1.0 × 0.5 deep	299	6.0	4.0 long 2.0 × 3.0 × 2.0 wide 1.0 × 1.5 × 1.0 deep
343	7.0	4.5 long 2.0 × 2.0 × 2.0 wide ? × 0.5 × ? deep	28	6.0	3.5 long 1.5 × 2.0 × ? wide 0.25 × ? × 0.5 deep
213	7.5	4.0 long 2.0 × 2.5 × 0.5 wide 0.5 × 1.0 × 0.5 deep	60	7.0	4.0 long 2.0 × 2.0 × 0.5 wide 0.5 × ? × 0.5 deep
337	7.5	5.5 long 3.0 × 4.0 × ? wide 0.5 × 0.5 × ? deep	3	7.5	4.5 long 2.0 × 2.0 × 3.0 wide ? × ? × 0.5 deep
331	8.0	6.5 long 5.0 × 5.0 × 1.0 wide 2.0 × 1.0 × 1.0 deep	119	7.5	5.0 long 2.5 × 2.5 × 1.0 wide 0.5 × ? × ? deep
260	9.0	5.0 long 4.0 × 4.0 × 1.0 wide 1.0 × 1.0 × 0.5 deep	329	8.5	3.0 long 2.0 × 2.0 × 1.0 wide 1.0 × 1.0 × 0.5 deep
220	9.5	3.0 long 0.5 × 1.5 × 0.5 wide 1.5 × 1.0 × 0.5 deep	120	9.5	3.0 long 1.0 × 1.5 × 2.0 wide 0.75 × 0.5 × 0.5 deep
2	Fibrillation on coronary ligature		320	Acute cardiac failure soon after ligature	
342	Fibrillation on coronary ligature		324	Specimen ill preserved	
340	Animal still alive		302	Specimen ill preserved	

*Length of heart taken from tip apex to a-v. groove left margin of heart.
†Length of infarct taken as maximum distance from apical end of infarct to basal end of infarct.
Width of infarct measured at 3 points from apex toward base of heart.
Depth of infarct measured at 3 points from apex toward base of heart.
Where measurement is very small "?" is substituted for a figure.

DISCUSSION

The above results support the contention of other authors that stellate ganglionectomy is not deleterious to the cardiac function of animals. The results further indicate that stellate ganglionectomy in the presence of coronary closure reduces the incidence of acute cardiac deaths and reduces the size of the resultant infarcts. The question arises as to how far these observations on the effects of deliberate coronary closure in healthy dogs can be applied to human cases of angina pectoris. At least it is fair to say that stellate ganglionectomy is not likely to be in the least harmful to the function of the heart and that, moreover, by cutting the nervous pathways concerned in the pain of angina pectoris, a definite part of the harmful mechanism will be destroyed. The nervous pathways which carry the painful impulses in angina pectoris form a real, and to the patient the most distressing part of the

syndrome; and they may perhaps, as pointed out below, act as a reflex arc which carries pain and other impulses centrally to return impulses to the heart which are deleterious to its function.

Just what sort of deleterious impulses may be carried to the heart over the sympathetic pathways that are connected to the heart through the stellate and upper thoracic ganglia is uncertain. The resting cardiac output of the dogs that had coronary ligation done without previous stellate ganglionectomy became elevated considerably and did not return to a preoperative level. It is possible that the myocardial infarct acted as an irritant stimulating the heart to greater activity through sympathetic overaction. The dogs with stellate ganglia removed prior to coronary ligation did not show any change in the resting cardiac output.

The dogs without ganglionectomy prior to coronary ligation exhibited an increased cardiac output at rest and showed larger infarcts at autopsy than the dogs with the stellate ganglia removed before the coronary ligation. It would appear that the same reflex that caused an increased resting cardiac output caused at the same time a coronary constriction with the production of a large infarct, or at least a lack of vasodilatory reaction about the infarcted area equal to that in the dogs with the stellate ganglia removed. Though it is true that increased cardiac activity usually presupposes an increased coronary flow, the larger coronary vessels do not necessarily dilate. It has not been demonstrated whether the increased coronary flow on cardiac acceleration is due to active arterial vasodilatation or merely to a more rapid flow through the arteriolar and capillary bed of the heart.

Furthermore, since dogs with stellate ganglia intact seemed much more susceptible to acute cardiac failure after coronary closure than dogs with the ganglia removed prior to coronary closure, it would appear that obliteration of the nervous pathways to and from the heart definitely protected the heart from some harmful influence. This circumstance seems comparable to those where spastic lesions in other parts of the body are benefited by section of the sympathetic pathways to the affected part.

The exercise cardiac output was not affected by coronary ligation in either group of dogs. This is accounted for by the fact that only moderate work was used in the exercise tests for reasons given elsewhere. This amount of work was such that the exercise response was not likely to be interfered with by the extent of coronary occlusion used in the experiments.[19]

On the whole it would seem not unfair to conjecture that, far from being a dangerous procedure in angina pectoris, bilateral stellate ganglionectomy or bilateral injection of the lower cervical and upper dorsal ganglia, would not only relieve the pain of angina without being dangerous, but would lessen the mortality of coronary occlusive lesions. It

would eliminate the sympathetic reflex arc, promote vascularization of areas threatened by anoxemia, and allow the heart absolute rest both by the relief of pain to the patient and by elimination of detrimental cardiac reflex responses to myocardial lesions.

SUMMARY

Twenty dogs, carefully trained and tested for resting and exercise heart rate, respiratory rate, blood pressure and ten for cardiac output, were subjected to coronary ligation of as similar nature as possible. Half the dogs were subjected, prior to coronary ligation, to bilateral stellate ganglionectomy at which time at least several of the upper dorsal ganglia were also removed.

The dogs with stellate ganglia removed were not affected by this procedure as judged by the above criteria of cardiac function. When coronary ligation was done, there was no change in the cardiac output, heart rate, respiratory rate, or blood pressure. Only one of the ten dogs died of acute cardiac failure. At autopsy the infarcts were all smaller than those found in hearts of similar size in the other group of dogs.

The dogs with stellate ganglia intact were quite definitely much more affected by coronary ligation. There was no great difference between the two groups in pulse, respiration or blood pressure, but resting cardiac output in this group became elevated considerably after coronary ligation and remained elevated. Five of the ten dogs died of acute cardiac failure very typical of the cardiac failure seen in human cases of coronary disease, and all of the hearts of this group exhibited larger infarcts than hearts of similar size in the other group of dogs.

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EXPERIMENTAL EXTRASYSTOLES ELICITED THROUGH ARTIFICIAL STIMULATION OF THE ENDOCARDIUM OF THE DOG*

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THE generally accepted interpretation of electrocardiograms supposed to represent the activity of the right and of the left ventricle has been subjected during the last few years, to a rigorous reexamination. This reexamination was stimulated chiefly by the work of Barker, MacLeod and Alexander who demonstrated that in man extrasystoles evoked by mechanical stimulation of the cardiac surface do not conform with the generally accepted characteristics of levo- and dextrocardiograms. Fahr, on purely theoretical grounds, had already expressed doubt as regards the validity of the interpretation of bundle-branch block. Oppenheimer and Oppenheimer arrived at similar conclusions as a result of a detailed study of a large number of bundle-branch block cases. These authors succeeded in demonstrating the inadequacy of Lewis' views upon the electrical representation of the left and right side involved in either type of bundle-branch block. Similar to Lewis, who based his views on clinical findings, these authors also based their evidence on clinical and more elaborate anatomicopathological investigation. Wilson, MacLeod and Barker applied a similar reasoning to the interpretation of preponderance curves.

Experimental investigations of the problem were completely disregarded, a fact which is not surprising in view of the divergent results obtained in animal experiments as regards localization by the electrocardiogram of the origin of artificially induced beats. Nevertheless, Roberts and his coworkers brought forward experimental evidence obtained in animals, after transection of one bundle-branch, which is in complete agreement with the results obtained by Barker on man.

As regards the investigation of extra beats no further systematic experimental studies on animals were reported. This is probably due to the fact that the results obtained by stimulation of the surface of the heart are usually not concordant. It is, however, necessary to mention that Barker's findings in man agreed at least with some aspects obtained by Rothberger and Winterberg on animal material.

It is generally accepted that the Purkinje system is the chief source of ventricular extrasystoles. Inducing extra beats by stimulation of the cardiac surface appears, therefore, as a most unnatural method

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for an experimental reproduction of spontaneous extrasystoles. In order to approach conditions which seem to prevail in the case of spontaneous extra beats, I endeavored to evoke extrasystoles in dogs by mechanical stimulation of the inner surface of the ventricular cavity.

Experiments were performed on large dogs, anesthetized with sodium phenobarbital or morphine. The slow heartbeat observed under morphine anesthesia was found helpful in the experiments. The electrocardiogram was taken with the Cambridge string galvanometer in the usual three leads, ordinary plate electrodes being introduced under the skin of the respective limbs. An ordinary Kodak cable release of an appropriate length was used for stimulation purposes. The cable release was introduced into the left ventricle through the carotid artery, and into the right ventricle through the right jugular vein, the thorax of the animal remaining closed. An appearance of sudden irregularities in the blood pressure curve, due to missed beats, indicates that the cable release has reached the ventricular cavity. It is then fixed, by tying a ligature round the respective blood vessel, in such a position that the cardiac contractions again become regular. Once the cable release is fixed, a pressure on its pushpin invariably evokes extra beats, provided that the pin reaches the endocardial surface and provided that the stimulus does not fall into the refractory period. Post-mortem examination clearly reveals the actual point which had been stimulated, as it appears as a pale spot or sometimes as a small blood effusion.

In experiments performed on twenty-six dogs I failed to observe even once electrocardiographic aspects which are usually alleged to represent the corresponding ventricle. Stimulation of the left ventricular endocardium gave rise to an extra beat which invariably displayed in Lead I an electrocardiographic aspect which hitherto has been considered to represent the right ventricular type. Inversely, right ventricular extrasystoles evoked by stimulation of the right endocardium gave in Lead I an electrocardiogram usually regarded as that of the left ventricular type. Lead III showed in the majority of cases a deflection in the direction opposite to that of Lead I, i.e., still displaying characteristics contrary to those which are generally accepted. Sometimes the main deflections in Lead I and Lead III were in the same direction, displaying, therefore, a concordant type and resembling some of the electrocardiograms obtained by Rothberger and Winterberg in epicardial stimulation.

Figure 1 shows a tracing obtained in the dog, in which left ventricular extra beats were evoked by stimulation of the corresponding endocardium. The extrasystoles display a downward deflection in Lead I and diphasic curves in Leads II and III, in the latter case the first Lead III a transition between a definite upward deflection as illustrated by Fig. 3 and a simple downward deflection, sometimes met with when the stimulus proves to have been applied near the apex of the heart. No such variations are presented by Lead I, which invariably shows with endocardially evoked forced beats a main deflection opposite to that which would be expected on the basis of the classical interpretation.

Right ventricular extrasystoles elicited through mechanical stimulation of the right endocardium, as shown in Fig. 2, display an upward directed deflection in Leads I and II and a downward directed main deflection in Lead III. Again, there may be some variations in Lead III, but Lead I invariably shows an electrical deflection which is the reverse of that generally looked upon as representing right ventricular extra beats. It is important to emphasize the constancy of

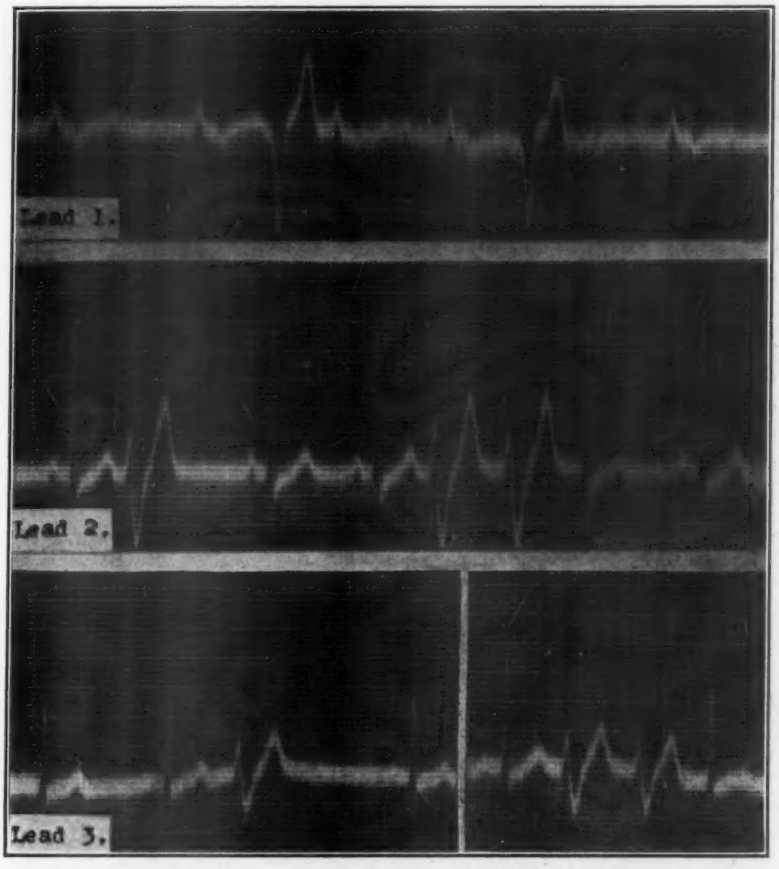

Fig. 1.—Left ventricular forced beats in dog weighing 24 kg. and anesthetized with morphine and phenobarbital. Cable release introduced into left ventricle. Canine electrocardiograms in the usual three leads, with string sensitivity 1 cm. corresponding to 1 mv. Horizontal lining in millimeters, vertical time marking in fifths of a second throughout all figures.

Left ventricular extrasystole of aberrant diphasic type, evoked through mechanical stimulation of the endocardium, interfering with the sequence of normal heartbeats.

the electrocardiographic aspects displayed by the extra beats induced by endocardial stimulation.

In some instances, extrasystoles which are induced by mechanical stimulation of the endocardium are followed by spontaneous extra beats; these display the same electrocardiographic aspect. Fre-

quently, under these conditions, groups of spontaneous extra beats of identical type can be evoked by occlusion of the aorta or by faradic stimulation of the extracardiac nerves. Figure 3 shows left ventricular extrasystoles with a downward deflection in Lead I and an upward deflection in Lead III. The first extra beat in each lead is forced through endocardial stimulation; the second is spontaneous. Both

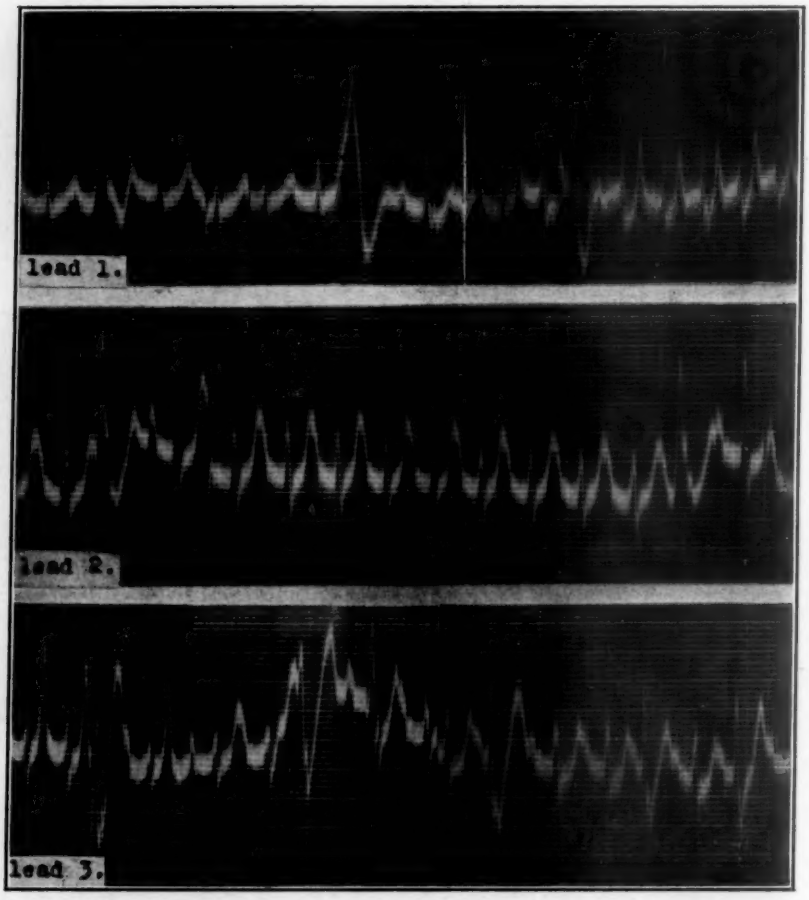

Fig. 2.—Right ventricular extra beats in dog weighing 22 kg. and anesthetized with morphine. Cable release introduced through jugular vein into the ventricle. Right ventricular extrasystole of aberrant diphasic type, evoked through mechanical stimulation of the endocardium, to be seen disturbing the normal rhythm in all three leads.

extra beats display almost identical aspects of their electrocardiographic records. The same happens in the case of right forced and spontaneous extra beats as can be seen from Fig. 4.

It is of interest that in normal animals spontaneous extrasystoles sometimes occur during a temporary occlusion of the aorta, display-

ing an electrocardiographic aspect which is identical with that observed in forced endocardial left ventricular extra beats.

There is a definite discrepancy between my observations and those of Rothberger and Winterberg, made with extra beats of epicardial origin. The following considerations should, however, be taken into account. Lewis has shown that an artificial wave of excitation initiated by stimulation of the cardiac surface, has to penetrate through the whole thickness of the muscle and reach the Purkinje network before it is picked up and conveyed to the whole lining of the heart. Lewis also states that in the case of the thick left ventricular wall the

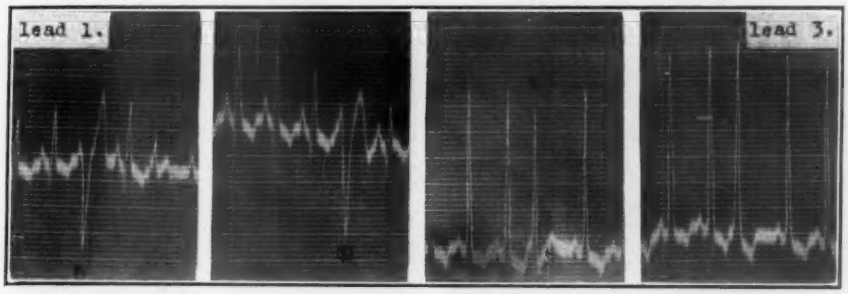

Fig. 3.—Dog weighing 18 kg., anesthetized with phenobarbital anesthesia. Electrocardiograms in Lead I and Lead III.
First premature beat interfering with the normal rhythm in each lead is forced through mechanical stimulation of the inner surface of the left ventricle. The second to be noticed in each lead is spontaneous; note its almost identical aspect.

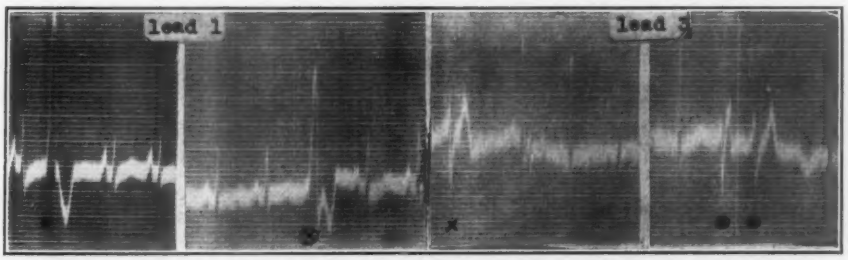

Fig. 4.—Dog weighing 23 kg., anesthetized by phenobarbital. Left group of records in Lead I, right group in Lead III.
First of each displaying an extrasystole elicited through mechanical stimulation of the right ventricular endocardium, the second, a spontaneous extrasystole with similar electrocardiographic aspect.

propagation rate is greater along the surface of the heart than across the muscle itself. Thus an excitation wave initiated by a stimulus which is applied to the surface of the left ventricle at a point not far removed from the interventricular septum may travel along the surface of the heart and penetrate through the thin wall of the right ventricle before it has time to penetrate through the thick wall of the left ventricle, the right Purkinje network being then stimulated first. Experimental support is to be found in the observations made by Wiggers on the spread of impulses originating from artificial heart

surface stimuli. Stimulation of the surface of the left ventricle may thus, in certain cases, evoke a right ventricular extrasystole. It is very likely that Barker happened to apply the stimuli to such points of the heart surface as did not lead to responses open to controversy and which definitely evoked extrasystoles of the corresponding type.

The method of eliciting ventricular extrasystoles through endocardial stimulation supplies further evidence against the usually accepted interpretation of the levo- and dextrocardiogram.

The results obtained are in complete agreement with the experimental and clinical evidence recently advanced in the literature.

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A STUDY OF THE ESOPHAGEAL LEAD IN CLINICAL ELECTROCARDIOGRAPHY*†

PART II. AN ELECTROCARDIOGRAPHIC STUDY OF AURICULAR DISORDERS IN THE HUMAN SUBJECT BY MEANS OF THE ESOPHAGEAL LEAD

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IN A recent communication[3] the theoretical and practical considerations pertaining to the use of the esophageal lead in clinical electrocardiography were subjected to critical assessment and the results of applying this method to 15 normal subjects and 35 patients with cardiac disease were noticed and discussed. A study has now been made of 92 additional clinical cases exhibiting abnormalities in the function of the auricles.

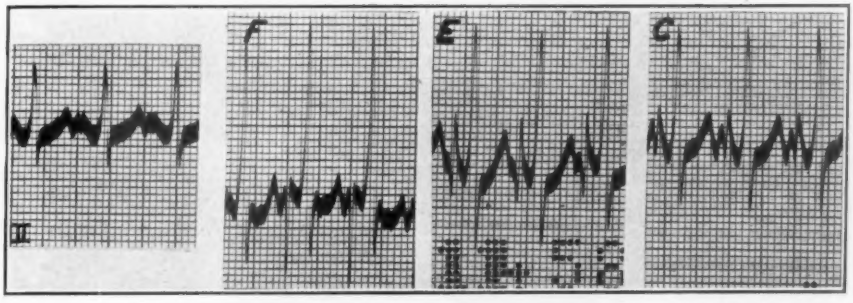

Fig. 1.§—Patient P. S. A case of simple auricular tachycardia. Lead II as designated. Curves F, E and C are esophageal electrograms from the regions indicated in Fig. 4A, part I.[3] Subsequently at a normal rate of heart action the esophageal lead yielded precisely similar complexes from these respective regions.

Owing to the diversity of conditions investigated in the present report, the subject matter has been divided into two parts: Section I is a miscellany comprising a variety of conditions—auricular tachycardia, mitral stenosis, hypertensive heart disease, myxedema and examples of hidden P-waves; Section II treats of auricular flutter and auricular fibrillation.

SECTION I

Auricular Tachycardia.—Four cases of auricular tachycardia were studied. Two were examples of simple sinus tachycardia, and two were paroxysmal in nature. The former (Fig. 1.) showed P-waves which were in all respects, apart from their rate, similar to the P-waves of

*From the Cardiographic Laboratory of the Johns Hopkins Hospital and University.
†Presented in abstract before the American Heart Association, Atlantic City, June 11, 1935.
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§Time: 0.04 sec. in all illustrations excepting those including two or three strings when it is 0.2 sec. Standardization: 1 mv. = 10 mm. unless otherwise specified.

the esophageal curves obtained in the same patients at normal rates of beating. The paroxysmal curves, on the other hand, were remarkable and merit further discussion.

The first example, taken from a man thirty years old who suffered from severe hyperthyroidism (B. M. R. +68), is illustrated in Fig. 2. Esophageal electrograms are shown from two auricular sites during the tachycardia and from the same points after the reversion to normal rhythm which followed thyroidectomy. The similarity of the form of

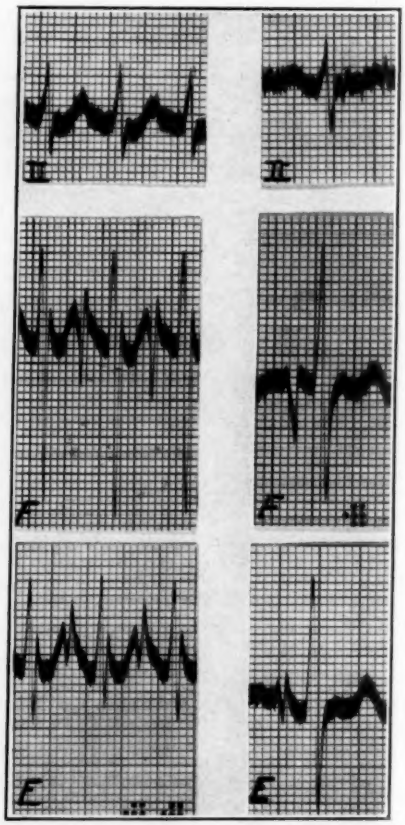

Fig. 2.—Patient H. D. Records from a case of paroxysmal auricular tachycardia taken during an attack and upon recovery. Lead II as designated. The esophageal records were obtained from the same auricular sites, respectively, at the two rates of beating. The letters on the esophageal curves refer to the regions marked in Fig. 4A, Part I.[3] A 2-to-1 heart-block is present. (See text for discussion.)

the P-waves at the two rates of beating, as taken from the same auricular areas, is strong evidence against an ectopic focus as the source of the tachycardia. If the responsible focus is ectopic it must lie extremely near to or, possibly, actually in the sino-auricular node.

There is an added and very important feature. The ventricle is responding to alternate beats of the auricle. The fact that a 2-to-1 A-V block is present is revealed on careful examination of the ventricular

complexes before and after recovery. In the normal or postoperative esophageal curves the upstroke of the S-wave merges smoothly into the beginning of the S-T segment, whereas in the curves showing tachycardia, there is an upwardly directed spike at the end of the S-wave. It is apparent also in one esophageal record that the hidden P-wave responsible for this abnormality varies slightly in its time of occurrence and alters the distribution of voltage in the QRS complexes by adding now to the R-wave and now to the S-wave. The rate of the auricle in this example must therefore be taken as being between 286

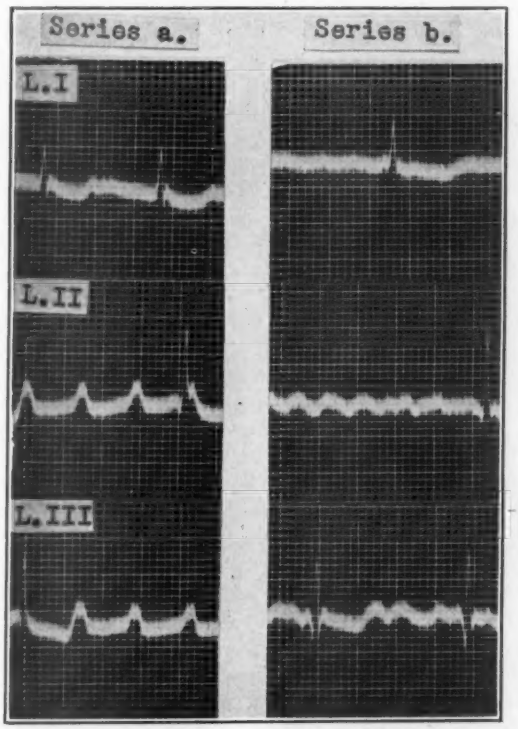

Fig. 3.—Patient S. F. Conventional Leads I, II, and III from a case of paroxysmal auricular tachycardia. Records of *Series a* were obtained during heavy digitalis administration; *Series b*, during a period of transitory auricular fibrillation before reversion to normal rhythm. (See text for full description of the case.)

and 300 beats per minute, a fact that was not suspected until after recovery, when the second esophageal examination revealed the true state of affairs.

The second case of paroxysmal tachycardia is of exceptional interest. Because it is believed to illustrate a very unusual clinical condition, it is deemed expedient briefly to describe the clinical history and findings.

The patient was a well-nourished, excitable, Jewish woman, aged forty years, who gave a vague history of rheumatic pains in childhood. From the age of seven, at which time she was told she had "heart trouble," she was subject to

exertional dyspnea. When she was thirty-two years old, she began to experience attacks of palpitation. The attacks began with lightning swiftness and subsided as quickly. At first these were of short duration but in January, 1935, the disorder became persistent. She had noticed that the attacks could often be terminated by holding her breath. At times there was severe substernal pain radiating to both arms, to the left shoulder blade, and to the neck. Swelling of the ankles, production of frothy blood-tinged sputum, and a terrifying feeling of weakness accompanied these episodes. She was admitted to the Sinai Hospital in Baltimore on Jan. 5, 1935, and a tentative, though disputed, diagnosis of auricular flutter was made. Auricular fibrillation was induced by the administration of a total of two grams of digitalis over a period of seven days. The fibrillation persisted for two days, after which spontaneous reversion to normal rhythm occurred. Figure 3 shows conventional records during the period of heavy digitalization and the period of auricular fibrillation.* The patient was discharged on Feb. 14, 1935, without continuance of digitalis therapy. Three weeks later (March 8, 1935) she was admitted to the Johns Hopkins Hospital in considerable distress and severe pain of the type described above. On examination the ventricular rate was counted at 107 per minute. Venous pulsations of the veins of the neck were readily discernible at about twice this rate. On four occasions in as many days the patient was prostrated for long periods with severe pain, great apprehension, dizziness, orthopnea, extreme cyanosis, accompanied by frothy, blood-flecked sputum. During these periods the radial pulse became over 200 to the minute and the venous pulsations uncountably rapid. Vagal pressure was responsible for an occasional dropping out of auricular complexes at this rate (1*a* in Fig. 4), but at the usually prevailing rate only a slight decrease in the rate of the ventricle was observed. Electrocardiographic tracings at the slow rate showed a 2-to-1 block, with an auricular rate of 214 and ventricular rate of 107 per minute. During the more severe paroxysms the tracings showed an exact doubling of both these rates. Digitalis therapy was instituted and continued despite the appearance of severe toxic symptoms until, when 2.1 gm. had been given in seven days, the rhythm reverted to normal. She was discharged on April 13, 1935, after a carefully graduated course of physical therapy and exercise, on a maintenance dose of digitalis. This was efficacious in preventing a reappearance of the arrhythmia for a period of five months.

The clinical diagnosis presented a problem of considerable difficulty owing to the presence of harsh systolic and diastolic murmurs at the pulmonary area and softer but independent double murmurs at the apex. There was considerable enlargement of both auricles and of the pulmonary conus. The possibility of pulmonary and mitral stenosis in the presence of a patent interauricular septum was entertained. The paroxysms were generally accepted by various clinicians as being due to auricular flutter.

The records of this case are shown in Fig. 4. Curves *1a* and *1b* show the conventional Leads II and III, respectively, at the fast rate (auricles 428 per minute). Of interest are the occasional instances of auricular block occurring during vagal pressure. This feature in association with the very fast rate at once throws suspicion on a diagnosis of auricular flutter. Curves *2a*, *2b*, and *2c* show the conventional Leads I, II and III and curves *2d*, *2e*, and *2f*, the esophageal electrograms at the usually prevailing rate of 214 auricular contractions per minute. Curves

*The writer is greatly indebted to Dr. Austrian and Dr. Katzenstein for their courtesy in permitting examination of the patient at the Sinai Hospital, for the permission to publish the records in Fig. 3, and for the opportunity of further study of the patient at the Johns Hopkins Hospital.

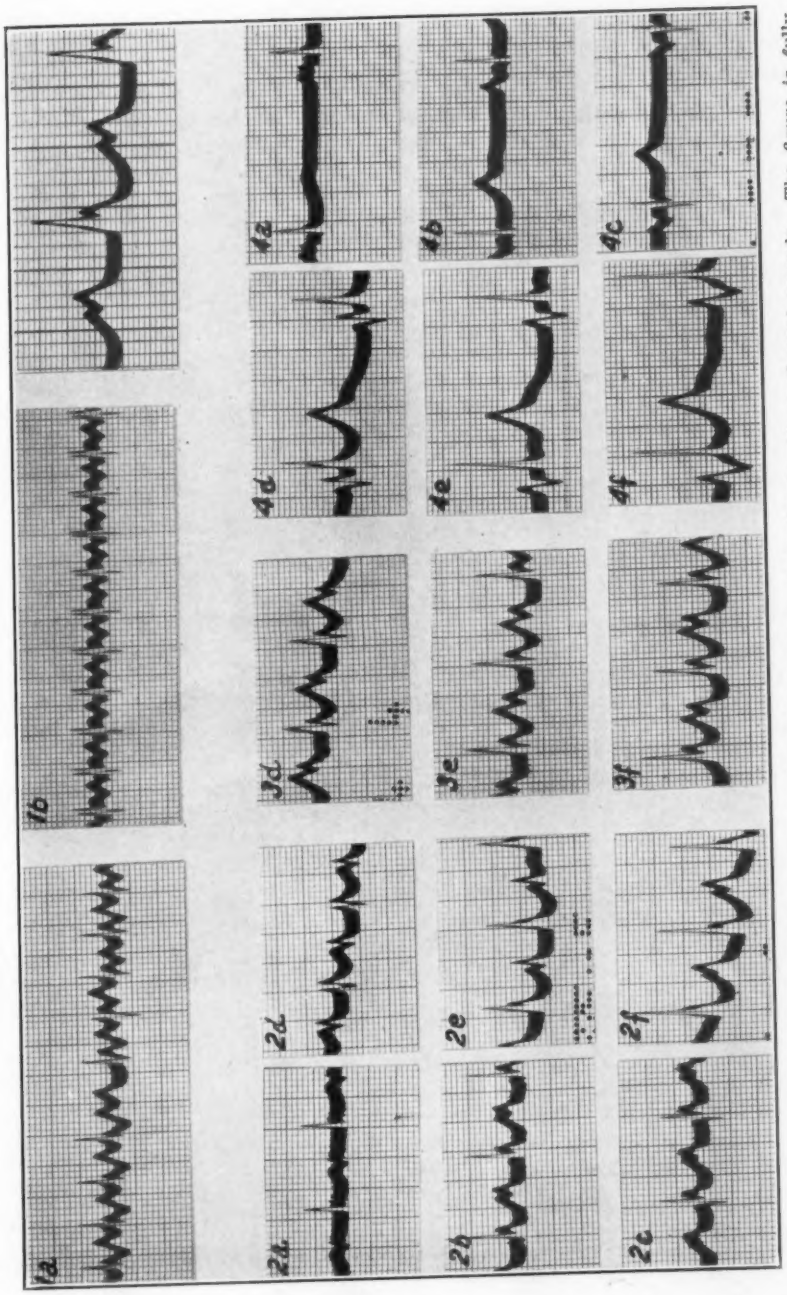

Fig. 4.—Patient S. F. Paroxysmal auricular tachycardia showing conventional and esophageal records. The figure is fully described in the text.

3d, *3e*, and *3f*, taken at the same rate, are esophageal electrograms taken near the height of digitalization while *4d*, *4e*, *4f*, and *4a*, *4b*, *4c*, respectively, are esophageal and conventional Leads I, II and III after recovery of normal rhythm. All electrograms here compared are from corresponding auricular sites. Series "d" are from the lower part (corresponding to region G in Fig. 4 A, Part I[3]). Series "e" are from a point 2 cm. above "d," and series "f," 2 cm. above "e." The unmarked esophageal curve photographed at double camera speed is taken at the habitual or persistent cardiac rate (auricles 214 per minute).

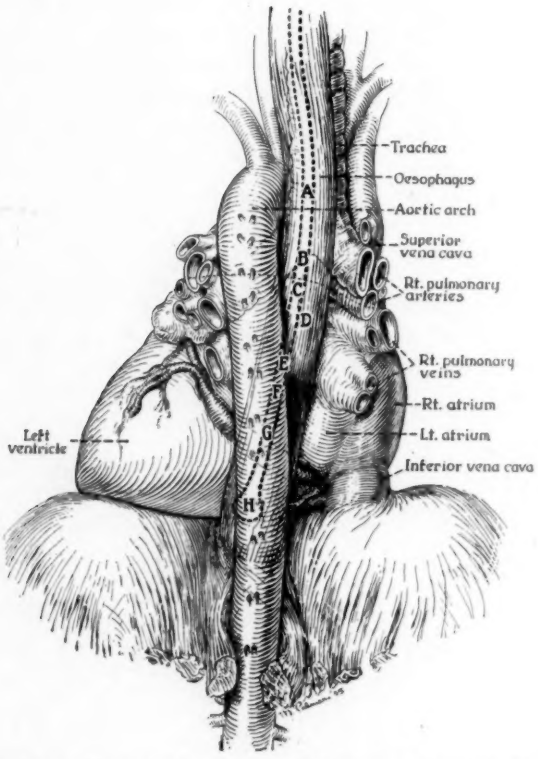

*Fig. 4A.—Drawing of a posterior surface of the human heart to illustrate the position of the esophagus in relation to the left auricle and the left ventricle. The lettered areas indicate the regions tapped by the electrode.

The conventional records have twice been erroneously diagnosed as auricular flutter. Certainly the combination of definite, if deformed, P-waves in the esophageal curves in the presence of an unmistakable return to the isoelectric line is proof that at the usually prevailing rate, 214 auricular and 107 ventricular contractions per minute, a 2-to-1 block of an auricular tachycardia was present. When the records of this and the preceding patient are compared with the examples of true flutter

*Reprinted from Brown, W. H.: A Study of the Esophageal Lead in Clinical Electrocardiography, Part I, AM. HEART J. 12: 1, 1936.

(Section 2), there can be no doubt that the mechanisms underlying the two conditions are quite dissimilar. This point receives additional stress in the later discussion of auricular flutter, but for the present these two cases are offered as evidence that 2-to-1 A-V block does occur in paroxysmal auricular tachycardia and that the auricular rate in this condition may rise, certainly to 300, and very probably as high as 428 beats per minute. The regrettable lack of esophageal electrograms at the faster rate makes certainty impossible, but the probability that the mechanism responsible is still that of paroxysmal tachycardia and not flutter is strengthened by the curious dropping out of auricular complexes seen in conventional Lead II (*1a* in Fig. 4) on vagal pressure. There also seems to be little doubt that the focus from which the abnormal rhythm arose is different from that responsible after normal rhythm was reestablished, but there is such gross deformity of the P-waves in both esophageal and conventional curves under conditions of normal rhythm that the matter cannot be settled with finality.

The markedly abnormal character of P-waves of the esophageal electrograms in this case is the subject of reference later in this report. A most remarkable feature in this connection is that, although the patient was examined on ten separate occasions, the only area of auricular muscle to yield defined intrinsic deflections in the auricular complex was the lower pole of the left auricle. If the electrode was raised 2 cm. above this area, despite the fact that the auricles were larger than normal, the P-complexes lost all trace of a sharply defined intrinsic deflection. The degree of P-wave deformity is best appreciated by comparing the curves under consideration with the normal curves of Fig. 4 B, Part I,[3] but the underlying cause of the deformity remains unknown.

Mitral Stenosis.—Samojloff and Steshinsky[31] long ago pointed out in cases of mitral stenosis that the character of the P-waves in conventional leads changes with the clinical condition. In a patient who had high P-waves, they observed that, as congestive failure developed, the P-waves became of progressively lower amplitude.

The first point of interest in the present study of twenty-four cases of suspected mitral stenosis with normal rhythm is to determine whether the height of the intrinsic deflection in the esophageal electrogram is greater when the amplitude of the P-wave of Lead II is increased. Figure 5 provides an answer to this query and is an example of a relationship found in nearly all cases uncomplicated by congestive failure. In general, a high or low P-wave in conventional Lead II yields respectively great or small amplitude of intrinsic deflections in the electrograms.

The twenty-four cases were divided into four groups: A, patients who had had rheumatic fever but who had neither a diastolic mitral murmur nor discernible enlargement of the left auricle; B, patients

who had diastolic mitral murmurs and slight enlargement of the left auricles; C, patients who had diastolic mitral murmurs, large left auricles but no sign of congestive failure; D, patients with mitral stenosis and in congestive failure. A study was made of the esophageal records in each of these cases. In every instance at least six such records were taken from the various auricular sites, and those which showed greatest amplitude in the P-waves were chosen for comparison with the normal control series.

Those cases which fell into Group A showed electrograms which could not be distinguished from the normal controls. Those in Groups B and C showed increased height of the intrinsic deflections as in Fig. 5. The cases in Group D all showed some, and often a very marked, diminution of the amplitude of the intrinsic deflections (Fig. 6).

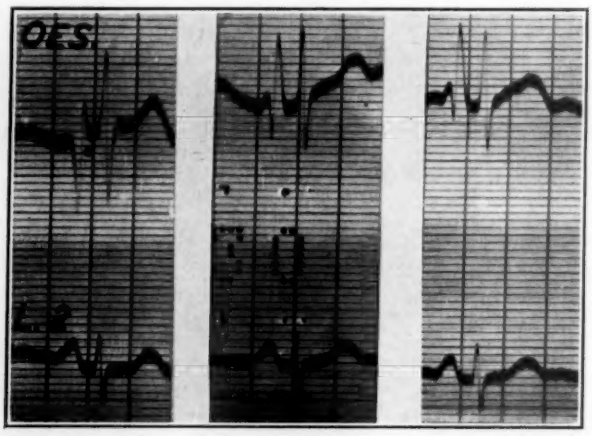

Fig. 5.—Patient H. M., with mitral stenosis. Simultaneous records from the esophageal lead and conventional Lead II to illustrate that high voltage P-waves in conventional leads are represented by an increased amplitude in the intrinsic deflection of esophageal electrograms.

In addition to these findings, another abnormality of the P-waves of the electrograms was frequently seen. This was a deformity or slurring of the extrinsic waves (see Fig. 4 B, Part I[3] for comparison). It occurred most frequently in Group D. The curves shown in Fig. 7 were obtained from a man who had on four separate occasions been admitted for congestive failure, with normal rhythm. He was the only patient in this series of cases of mitral stenosis who developed auricular fibrillation and in whom a comparison could be made of the electrograms in both rhythms. Of like importance was the case of mitral stenosis considered in the section on auricular tachycardia (Fig. 4). In the records obtained after normal rhythm was reestablished there was only one auricular site which yielded electrograms showing no serious deformity of the P-wave. In the other two esophageal curves which were obtained when the electrode was contiguous to the middle

and upper portions of the dilated left auricle, striking deformities of the wave were present.

On the slender evidence which these few cases provided, it is manifestly impossible to arrive at definite conclusions. It is, nevertheless, fair to suggest that these gross deformities of the P-wave of the electrogram indicate interference with the even spread of the excitation wave. No post-mortem evidence is as yet available to aid in the interpretation of what these changes mean in terms of the underlying pathology of the auricle. It can only be said that deformities of this character preceded by four months the onset of auricular fibrillation

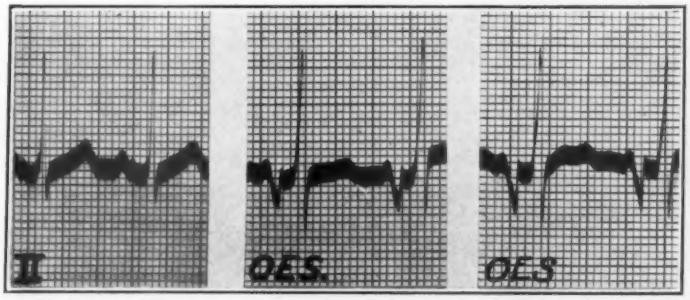

Fig. 6.—Patient L. F. From a case of mitral stenosis. Lead II and two examples of esophageal leads. The latter show decreased amplitude of the intrinsic deflection with slurring of the extrinsic portions of the complex.

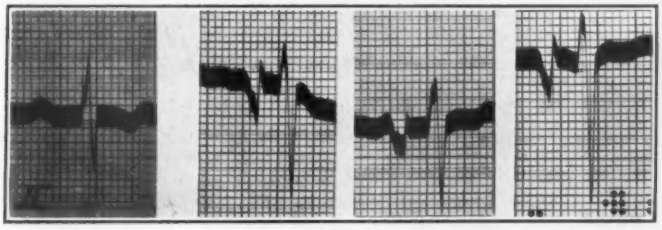

Fig. 7.—Patient T. G. Lead II and three esophageal leads from a case of mitral stenosis in congestive failure. The esophageal curves show marked slurring of the extrinsic parts of the complex. (See text.)

in one case and that they both preceded and followed attacks of very rapid tachycardia (up to 428 per minute) in the other. The facts do, however, give grounds for the belief that a wider use of the esophageal lead in cases of mitral stenosis would soon yield evidence of considerable prognostic value.

Hypertension.—Increased amplitude of the P-waves of conventional leads is most commonly found in pulmonary and mitral stenosis and in hypertension.[1, 25, 34]

Esophageal leads have been taken in twenty-eight cases of hypertension. It may be said that the same general relationship between the height of the intrinsic deflection of the esophageal electrograms and the

amplitude of the P-wave in Lead II holds here as in mitral stenosis. The appearance of congestive failure has also much the same effect in diminishing the amplitude of the intrinsic deflections.

There are, however, certain differences between the auricular electrograms in the two diseases. In severe hypertension the intrinsic deflections start far below the isoelectric line and seldom rise much above it (Fig. 8), whereas in mitral stenosis the greater part of the intrinsic deflection usually lies above the isoelectric line. The initial belief that both the distinctive character and the increased amplitude were dependent upon the actual degree of hypertension (blood pressure levels) has been proved to be unsound. The entire series of 142 cases was then reexamined to discover the clinical associations of the occurrence of P-waves of this particular type. Eighty per cent (22 cases) of those which showed such P-waves had diastolic pressures of over 110 mm.; the remainder had diastolic pressures ranging from 107 to 55 and included two cases of severe aortic insufficiency. On the other hand,

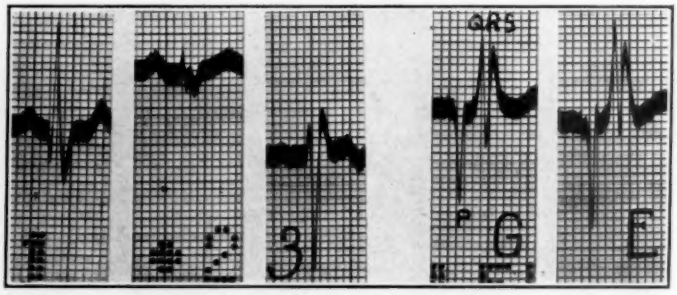

Fig. 8.—Patient E. C. From a case of severe hypertension showing the characteristic type of P-wave in the esophageal electrograms in this condition. There is also a splitting of the QRS complex which is probably indicative of intraventricular delay. The letters *G* and *E* indicate the levels of the esophageal electrode in terms of Fig. 4A, Part I.[3]

some cases of early, though severe, hypertension did not exhibit the type of P-wave under discussion.

After further investigation it has been found that the downwardly projected P-waves of the electrogram occur in the presence of great enlargement of the left ventricle. With the discovery of this common denominator the temptation is strong to suggest the following explanation of the findings: If, in the absence of enlargement of the left auricle, the left ventricle is enlarged sufficiently to displace the heart backward and, by its impingement on the chest wall, to the right; then the total effect is a relative "displacement" of the esophagus to the left. This change in turn causes an increase in the amount of auricular musculature lying between the esophageal electrode and the sino-auricular node. The net result is, therefore, a displacement of the intrinsic deflection, for any given esophageal site of the electrode, to a position relatively later in the P-wave than would normally be the case.

The wave "*e*" (Fig. 5, Part I[3]) is therefore prolonged and the wave *i* starts and finishes, respectively, lower and later than usual.

The experimental basis for the above theory is implied in the work of Lewis, Meakins, and White.[18] Further confirmation is presented in Fig. 9, taken from an experiment on a dog weighing 11 kg. The operative and galvanometric details are similar to those described in Part I, Fig. 2.[3] The leads are also similar except that in this experiment two direct leads (by wool extensions from nonpolarizable kaolin-saline copper-sulphate electrodes) were fixed to the right auricle, and each galvanometric circuit was completed through indifferent electrodes on the left

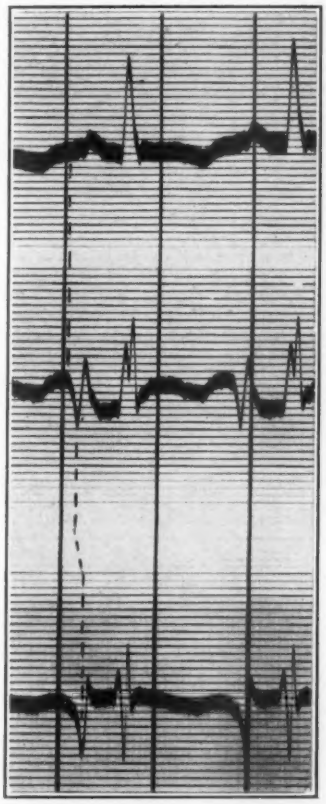

Fig. 9.—Conventional Lead II and two direct leads from the surface of a dog's right auricle, taken simultaneously. Fifteen millimeters of auricular muscle separated the electrodes from which the middle and the lower records were obtained. The delay in the onset of the intrinsic deflection is indicated by the lower dotted line. (For further details see text.)

hind leg. The lower curve is taken from an electrode placed near the base of the right auricular appendix and the middle curve from an electrode 15 mm. nearer the tip of the appendix. Upward deflections in the records indicate electronegativity of the direct electrodes. Lead II is shown above.

The intrinsic deflection of the direct lead taken farthest from the sino-auricular node occurs 0.0184 sec. later than the intrinsic deflection from the body of the auricle and begins far below the isoelectric line. The differences in time of occurrence and in form of these two intrinsic

deflections are attributable solely to the fact that excitation at the distal electrode occurred later than at the proximal. This in turn is due to the fact that the proximal electrode was about 15 mm. closer to the sino-auricular node than was the distal electrode.

This hypothesis was also put to a simple clinical test in five normal subjects. The esophageal electrode was passed to a depth at which it lay in a position corresponding to region F (see Part I, Fig. 4 A^2). Records were then taken with the subject lying first on the back and then on the right side. Comparisons of the records in each instance consistently showed a slightly later and lower onset of the intrinsic deflections when the subject was in the lateral posture than was seen in those records obtained in the supine position. The intrinsic deflections also did not rise as high above the isoelectric line when the patient was lying on the side. These findings were attributed to a shift of the heart to the right, resulting in a relative though slight displacement of the esophagus to the left.

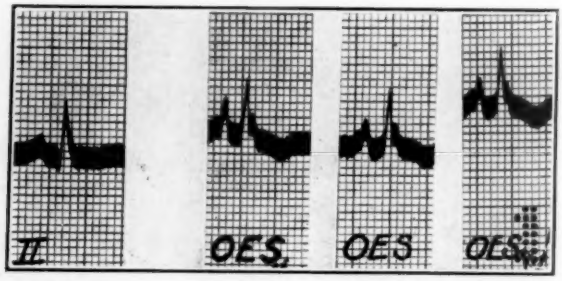

Fig. 10.—Patient O. G. Conventional Lead II and three esophageal curves. Case of myxedema. B.M.R. = -30. Note that there are no intrinsic waves in the esophageal electrograms and that the voltage remains low in these records. All curves standardized 1 mv. = 10 mm.

Myxedema and Hyperthyroidism.—Only four cases of myxedema and five of hyperthyroidism are included in the present series. It is not proposed in this report to discuss at length the findings in hyperthyroidism apart from those instances in which the condition is associated with particular arrhythmias. The P-waves of the hyperthyroid patients with normal rhythm show an apparently normal contour, with an amplitude of the intrinsic waves within the upper range of normal findings. Certain peculiarities of detail may be reported at a later date, but the findings have not yet been subjected to full experimental proof.

Zondek,[36] in his original paper, pointed out that low or absent P-waves were a characteristic of the myxedematous heart. After the controversy over the cause of the low voltage in electrocardiographic curves in myxedema (Leug,[10] Means, White, and Kranz[22]), this finding was relegated to obscurity from which it has been recently revived by Tung[33] and Hallock.[8]

In the myxedema cases of this series there was a remarkable distortion of intrinsic deflections of the P-waves in esophageal electrograms.

In one instance this appeared in the absence of either clinical or radiological evidence of enlargement of the heart. In the only case (Fig. 10) which showed low voltage in conventional leads, and in which great enlargement of the heart was present, not only were the P-waves greatly deformed but there was no increase in the voltage of the ventricular curve in the esophageal records.

Although the number of cases investigated is very small, the results suggest that not only is the low voltage of myxedematous hearts to be explained on a basis of an inherent defect in the myocardium and not to increased skin resistance, but also that one of the earliest signs of "myxedema heart" is to be found in decreased voltage and slurring of the intrinsic deflection of the auricular complex in esophageal leads.

The Use of the Esophageal Lead in the Discovery of Hidden P-Waves. —In the experience of everyone who has studied large numbers of

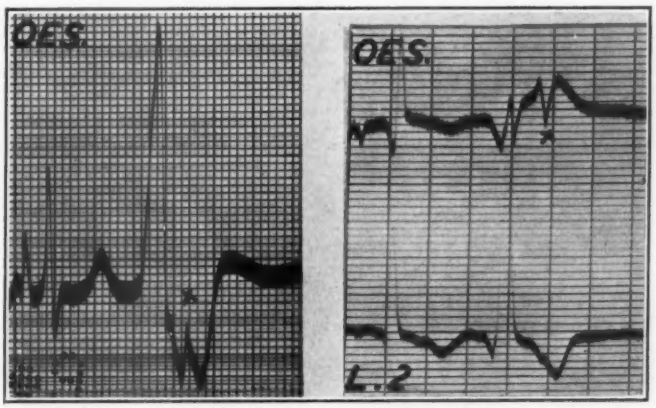

Fig. 11.—Patients S. A. and P. S. Two examples of retrograde P-waves shown hidden in the T-waves of ventricular extrasystoles are indicated by crosses. In the double record the esophageal lead shown above has been obtained with the electrode below the level of the left auricle. In the single string record the esophageal electrode lies near the upper pole of the left auricle.

electrocardiographic tracings, there occur instances when it is virtually impossible to be certain of the position and presence of the P-wave. In the present series a few interesting examples of this have been encountered. Mention has already been made of one case of auricular tachycardia in which the use of the esophageal lead supplied evidence of a decisive character (Fig. 2). Two additional examples merit illustration.

In Fig. 11 are shown two examples of hidden P-waves occurring as the result of retrograde excitation of the auricle in cases of ventricular extrasystoles. The character of these P-waves clearly denotes their ectopic origin. A curious feature of retrograde P-waves as seen in the esophageal curves is also illustrated, namely, the remarkable amplitude and definition of the waves, when compared with those of sinus origin. It has already been shown (Fig. 4 B, Part I[3]) that, when the esophageal

electrode is situated below the level of the lower pole of the left auricle, the P-waves lose their intrinsic deflections and become poorly defined. It is to be anticipated that retrograde P-waves would undergo similar

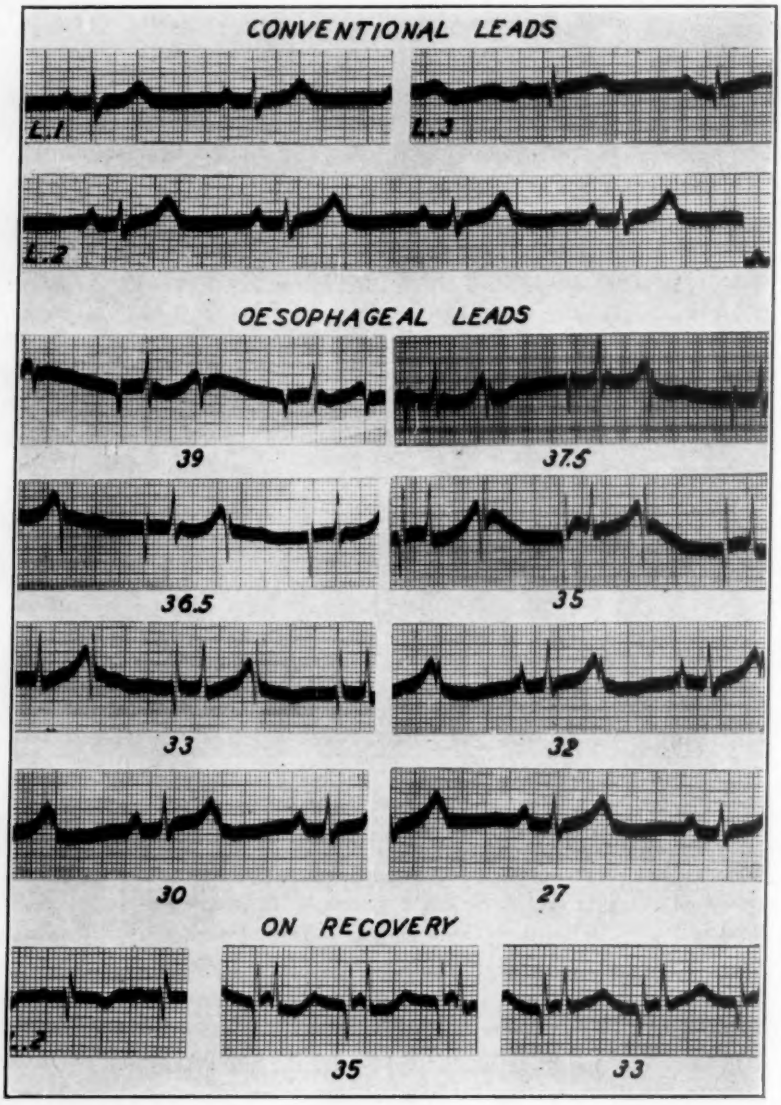

Fig. 12.—Patient E. L. Conventional and esophageal leads taken from the same patient at two different rhythms. Conventional leads during 2-to-1 block are indicated above. The segregated eight records in the central part of the figure are esophageal leads obtained with the electrode at the depth in centimeters indicated below each record. The lower line shows Lead II and two esophageal electrograms on recovery of normal rhythm.

changes. This appears, however, not to be the case, for this type of wave as well as certain other types of ectopic P-waves remains sharply defined in electrograms obtained from the ventricle. It is difficult to

provide a convincing explanation of this fact though the possible early excitation of the sleeve of musculature on the inferior vena cava may be the cause.

Another, though not quite perfect, example of hidden P-waves is shown in Fig. 12. The practice of showing only sample curves, which has, in the interest of space, been followed in other examples, is here departed from, and esophageal curves from all levels of the electrode are included. This serves not only as a demonstration of the way in which the method has been applied to the subjects of the series as a whole, but is instructive in showing the abrupt change in the character of the P-wave once the electrode has lost its proximity to the auricle.

From a cursory examination of the conventional curves the diagnosis is extremely likely to be one of first degree heart-block, but closer scrutiny leads to the detection of abnormalities in the form of the T-waves of Lead II. The esophageal curves give a clear explanation of this small discrepancy and establish the diagnosis of 2-to-1 heart-block beyond all doubt. After the upper limit of the auricle has been passed (between positions 33 cm. and 32 cm.), there is a rapid return of the P-wave to obscurity, and in the last position (27 cm.), where the electrode is lying near the arch of the aorta, the curve is very like that of conventional Lead II.

Recapitulation of Section I

The value of the esophageal lead lies in its exploratory principle. Its application in this capacity to the left auricle produces electrograms of a perfectly definite nature: the P-waves having an increased amplitude, a polyphasic form, and showing an intrinsic deflection. In a comparative study of the form of the waves under conditions of disease, decisive evidence has been forthcoming in regard to the distinctive character of auricular tachycardia as contrasted with auricular flutter. So far as functional disturbances of the auricle are reflected in electromotive changes, the esophageal lead is of great value in detecting the latter. In a limited number of cases of mitral stenosis and of myxedema the findings have strongly suggested that a wider use of the method might soon produce information of diagnostic and prognostic importance. The use of the method for the discovery of hidden P-waves has been demonstrated.

Summary of Section I

The esophageal lead has been employed in a study of certain abnormalities of the auricular complexes and of the rhythmic function of the auricles in sixty-seven human subjects.

Esophageal (auricular) electrograms from patients illustrating the following conditions have been reproduced and discussed.

Auricular tachycardia; simple sino-auricular and paroxysmal types (the latter showing 2-to-1 heart-block).

Mitral stenosis of varying grades of severity.

Hypertensive heart disease.

Myxedema and hyperthyroidism.

Hidden P-waves in heart-block and retrograde excitation from ventricular sources.

SECTION II

The Esophageal Lead in Clinical Cases of Auricular Flutter and Auricular Fibrillation

From an electrocardiographic point of view the outstanding contribution of the esophageal lead is the demonstration of the intrinsic deflection of cardiac action currents in the living human subject.[3] This characteristic of esophageal electrograms has been recognized by Lieberson and Liberson,[19] who were the first to publish a clinical record obtained by the lead. The importance of the finding lies in the fact that the method thus spans the gap between clinical electrocardiography and the results of animal experimentation. The hypotheses advanced to explain the various cardiac disorders as detected by indirect clinical leads are almost without exception based upon experiments on the exposed hearts of various other mammals. The transference of such results to the human subject has, in general, stood the test of time, but it has always, and legitimately, been open to a certain measure of doubt. This has been notably the case in regard to auricular flutter, auricular fibrillation, and the allied arrhythmias; for such disorders are usually the expression of disease, often of long standing, in the human subject. Conditions very like, if not identical to, them may be reproduced in healthy experimental animals by an appropriate technic. The question arises whether the experimental findings and theories based upon such findings are wholly applicable to the human subject.

Fibrillation has been observed occurring as the result of disease in horses[12] and dogs[27] on direct examination of the auricles of the exposed hearts. The gross appearances are very similar to auricular fibrillation as seen in the experimental animal. Fluoroscopic observations of the auricles in human subjects suffering from auricular flutter yield appearances indistinguishable from those seen in experimental animals. The strongest evidence brought in support of the thesis that the conditions occurring in man are identical to those produced in animals has, however, been obtained by the electrocardiograph. Lewis and his collaborators[17] have shown that a distinctive form is characteristic of auricular flutter waves obtained by leading directly from the auricular surface in dogs. They have shown that indirect leads obtained from such animals are indistinguishable in character from those occurring in conventional leads in human cases of auricular flutter. Moreover,

they have advanced[13, 14, 15] well-founded evidence in support of the theory that in both animals and man auricular flutter is due to a mechanism characterized by a single excitatory wave progressing with a "circus movement."

It is no part of the objective of the present report to attempt to prove or disprove accepted hypotheses. The facts which are offered are of interest because they supply one missing link in the above cited chain of evidence. The importance of such evidence as is offered is magnified by the fact that most observers believe auricular flutter, impure flutter, and auricular fibrillation are due to the operation of a common fundamental mechanism.[11, 2]

Auricular Flutter.—Four cases of auricular flutter were studied by the esophageal lead. They all differed with respect to etiology, and, as all recovered normal rhythm, a comparison was possible between curves obtained from the same auricular sites during and after the attack.

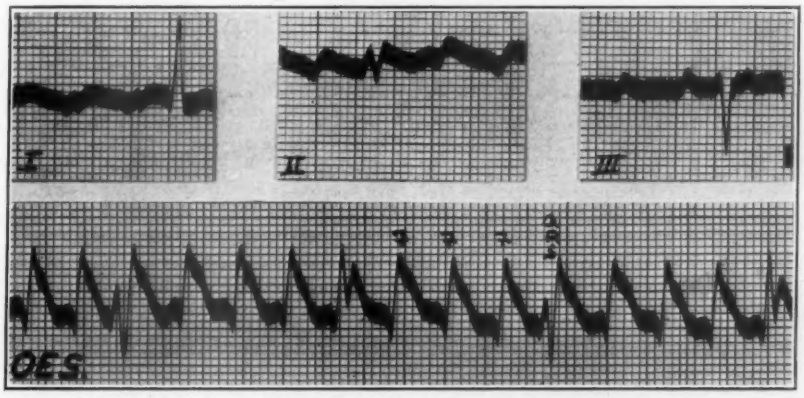

Fig. 13.—Patient W. E. Case of auricular flutter showing conventional Leads I, II, and III and an esophageal record. Flutter waves marked *F*. Standardization in each case 1 mv. = 10 mm.

The first patient was a busy executive aged fifty years who had neither history nor sign of rheumatic disease or of hyperthyroidism. He was severely arteriosclerotic but exhibited no hypertension. Flutter developed during a grave physical and mental breakdown apparently the result of overwork and strain.

In Fig. 13 conventional and esophageal curves are shown taken during the period of flutter. The character of the flutter waves is remarkably different from the normal type of P-wave and may with advantage be contrasted with those of simple auricular tachycardia (Fig. 1). The waves have a great amplitude, quite overshadowing, in some curves, the ventricular complexes. The stride of the waves is very long, one wave being terminated as the next begins.

After recovery on quinidine therapy the P-waves, where they occur (Fig. 14), show a prolongation of both the duration of the intrinsic

deflection and the whole P complex. Both these factors may be due to subnormal conductivity in the auricular tissue. Here and there the P-waves are completely absent, and the rare condition of sino-auricular standstill is seen, caused in all probability by the heavy dosage of quinidine (14.7 gm. over a period of nine days).

The second case was a thirty-year-old man who had a severe grade of hyperthyroidism (B. M. R. up to +88). Conventional and comparable esophageal curves before and after spontaneous recovery following thyroidectomy are shown in Fig. 15. The great difference between the character of flutter and normal P-waves is again illustrated in this case.

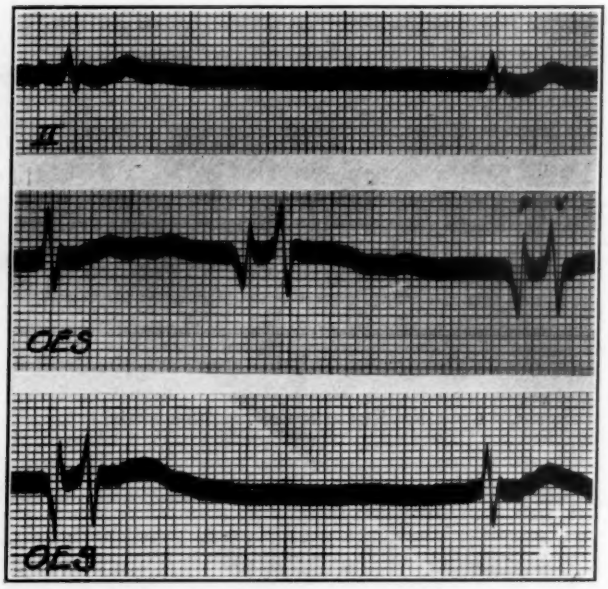

Fig. 14.—Patient W. E. Conventional Lead II and two esophageal records from the same subject as Fig. 13, after flutter had disappeared on quinidine therapy. The esophageal electrogram shows an example of auricular standstill with ventricular escape. The P-waves have a longer duration than normal. P-waves indicated by *P*, QRS complexes by *V*. Standardization 1 mv. = 10 mm.

These two examples leave no reasonable doubt that an abnormal and characteristic mechanism underlies auricular flutter. The esophageal electrograms of both show a close resemblance to the experimental curves of Lewis and his coworkers[17] from the dog* They afford a clear indication that flutter occurring in the human subject is similar to that produced artificially in dogs.

The third case of flutter was paroxysmal in nature. It occurred in a man fifty-five years old who had suffered from occasional prostrating attacks of tachycardia over a period of nine years. His history was

*Lewis' curves were obtained by double direct electrodes on the auricle in contradistinction to those derived with the esophageal lead.

noncontributory from an etiological point of view. He showed no signs of arteriosclerosis, hyperthyroidism, or mitral stenosis. On numerous occasions electrocardiographic investigations had been made without an accurate diagnosis being attained. He had acquired an addiction to morphine derivatives as a sequel to the frequent therapeutic use of these drugs for his disability. The curves here presented were obtained during and after a brief attack which occurred at the Johns Hopkins Hospital while he was under treatment for drug addiction.

Figure 16 shows the conventional Lead II and esophageal leads taken simultaneously. Apart from the decisive evidence given by the eso-

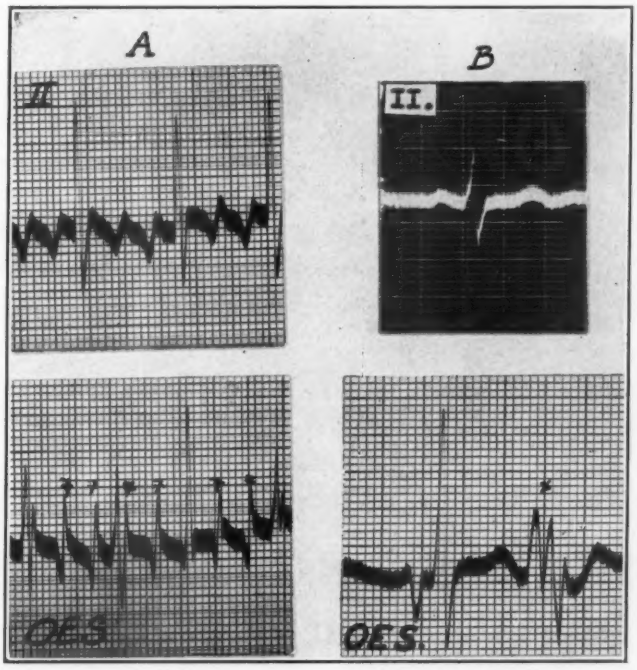

Fig. 15.—Patient W. D. Case of auricular flutter due to hyperthyroidism (Series A) and after recovery of normal rhythm (Series B). The conventional Leads II are indicated above, and esophageal electrograms taken from respectively the same auricular sites are shown below. Esophageal record taken during normal rhythm shows a ventricular extrasystole and slightly deformed P-waves. The patient showed signs of myxedema when the curves of Series B were obtained.

phageal lead in determining the correct diagnosis, there is an additional point of importance. Examinations of the curves show that the rhythm is a regular 2-to-1 flutter, the auricles beating at 300 and the ventricles at 150 per minute. A comparison of the time relationships between the intrinsic deflections in esophageal curves and the upstroke of the flutter waves in Lead II reveals progressive differences. As the electrode is moved downward to successively lower auricular sites, the intrinsic deflections in the electrograms become progressively earlier in occurrence

with respect to both the R-waves and the upstroke of the flutter waves in Lead II (as is indicated by the vertical dotted lines in Fig. 16). The actual times of occurrence of the intrinsic deflections are shown in Table

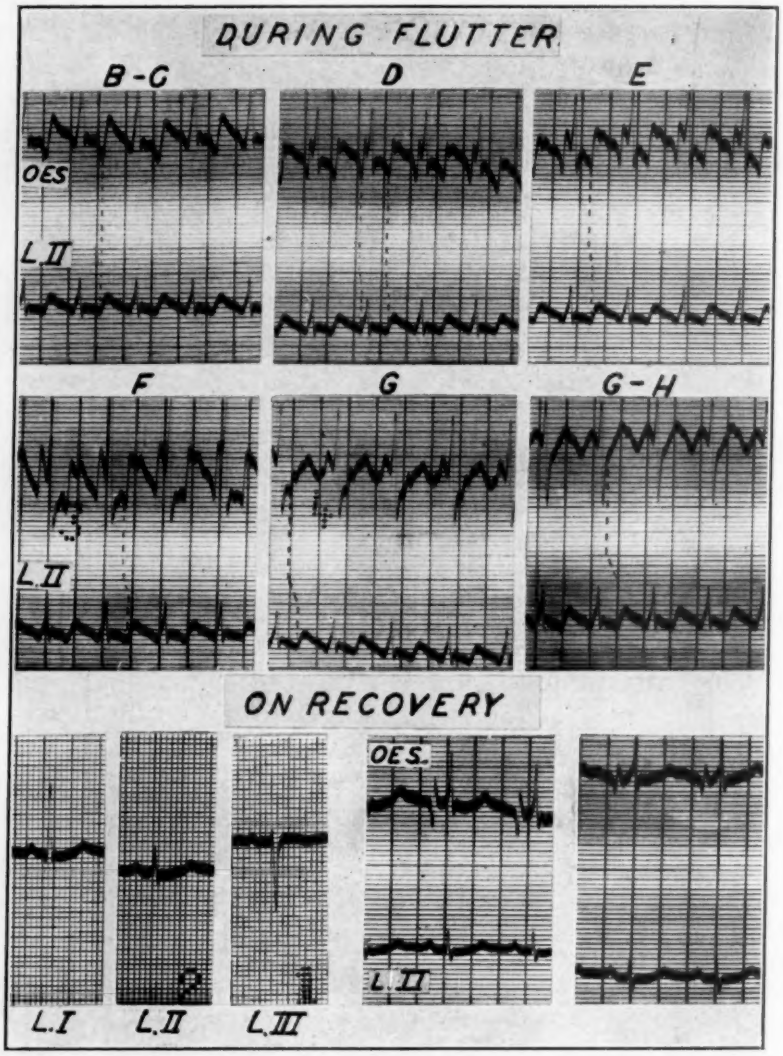

Fig. 16.—Patient D. R. From a case of paroxysmal auricular flutter during the attack and on recovery. Analysis of flutter waves is shown in Table I. The letters above the records in flutter indicate the position of the esophageal electrode in terms of Fig. 4A, Part I.[3] The dotted lines indicate the progressively changing relationships of the intrinsic deflections in the esophageal electrograms to the onset of flutter waves in conventional Lead II. Examples of conventional curves and of esophageal electrograms after recovery are shown below. (See text and Table I for discussion and data.)

I. It is apparent that in the region of the superior vena cava and the uppermost portion of the auricle the intrinsic deflections arise slightly later than the corresponding upstroke in Lead II. In the midcaval re-

gion, on the other hand, they are earlier by 0.0294 sec., while lower down, near the inferior vena cava, they occur 0.0734 sec. before the flutter wave of Lead II. This finding stands in contrast to the position of the intrinsic deflection in the P-complexes of normal curves (see Fig. 4 B., Part I[3]), where the earliest intrinsic deflections are obtained when the electrode is closest to the sino-auricular node. For positions of the electrode above and below this point (contrast curves *C* and *E* with *D* of Fig. 4 B, Part I[3]) the intrinsic deflections are always later with respect to the onset of the P-wave. The data of Table I quite definitely show that the flutter wave activated the inferior part of the left auricle about 0.06-0.08 sec. earlier than the upper part of the auricle. In other words, important evidence is here provided to augment that of Lewis[13] and his collaborators[15] to the effect that auricular flutter is due in man to a "circus movement." Under the conditions imposed by the esophageal method, only the left auricular segment of the circus pathway can be investigated. The findings here reported lose none of their significance if it is held that the areas tapped are not necessarily on the actual path of the "central" or "mother" wave, for the times of occurrence of the centrifugal waves are dependent upon the time of excitation of the contiguous central path.

In the section on paroxysmal auricular tachycardia (Section I) two unusually interesting cases of 2-to-1 block were discussed. The second of these cases (Fig. 4) on occasion exhibited an auricular rate of 428 per minute. Although esophageal electrograms were not obtained at the faster rate, the diagnosis of paroxysmal auricular tachycardia was entertained for reasons which were discussed at some length.

At this point it is expedient to point out why both of the cases cited cannot be considered to be due to auricular flutter. The curves from three undoubted cases of auricular flutter have been recorded above. The esophageal electrograms of these cases show a perfectly distinctive character, and are explainable only on the basis that the auricle is in a condition of continuous excitation. There is no return to the isoelectric line and no indication that the auricles are at any time electrically quiescent. The intrinsic deflections are followed by long extrinsic periods. Now the curves of the two cases of paroxysmal auricular tachycardia exhibit quite different characters. The auricular complexes, though grossly deformed in one case, are distinctly to be separated one from another and are easily recognizable as being periodically produced P-waves. In those instances in which the ventricular complexes do not interfere there is clearly a return of the curve to the isoelectric line. The mechanism underlying these arrhythmias cannot be the same as that responsible in auricular flutter.

Auricular Fibrillation.—Historical reviews and discussion of the various theories which have been advanced to explain the fundamental causes of this irregularity are to be found in the publications of Garrey[6]

TABLE I

COMPARATOR ANALYSIS OF THE FLUTTER WAVES OF FIG. 16 (AVERAGE VALUES)

	POSITION OF THE ELECTRODE			DURATION OF THE FLUTTER WAVE (SEC.)	TOTAL DURATION OF 3 SUCCESSIVE FLUTTER WAVES (SEC.)	TIME OF ONSET OF DESIGNATED (SEE FIG. 16) INTRINSIC DEFLECTIONS AS COMPARED TO THE SUCCEEDING R-WAVE (SEC.)	TIME OF ONSET OF THE INTRINSIC DEFLECTIONS IN ESOPHAGEAL CURVES COMPARED TO THE ONSET OF FLUTTER WAVES IN LEAD II OF A SIMULTANEOUS RECORD (SEC.)	
	DEPTH FROM TEETH (IN CM.)	AS ILLUSTRATED IN FIGURE 4 A PART I[3]	REGIONAL RELATIONSHIP TO THE AURICLE				PRECEDES BY	FOLLOWS BY
Standard Lead II	--	--	--	0.2065	0.6198	0.2591	0	0
Esophageal Lead	30	Above C	Above the left auricle	0.2060	0.6194	0.2490	--	0.0102
	32.5	B – C	Near the upper pole of the left auricle	0.2070	0.6202	0.2593	--	0.0044
	34	D	Upper region of left auricle	0.2069	0.6200	0.2743	0.0150	--
	36	E	Near the middle region of left auricle	0.2061	0.6191	0.2879	0.0294	--
	38	F	Below the middle region of left auricle	0.2067	0.6204	0.2970	0.0380	--
	40	G	At lower pole of left auricle	0.2050	0.6208	0.3330	0.0734	--
	42	Below G	Below auricular tissue	0.2050	0.6210	0.3431	0.0860	--

and of Lewis.[11] A brief restatement of the more popularly accepted theories will satisfy the purposes of this report.

There is almost complete unanimity in the view that auricular flutter and auricular fibrillation are closely related, often interchangeable, and hence probably caused by variations in the operation of a similar underlying mechanism. The chief premises of debate are therefore largely concerned with theories and speculations as to the nature of the responsible mechanism. The main theories which still claim devotees are three in number. Common to all of them is the conception that a state of disturbance in the conductivity and the refractory phase of auricular musculature with the production of varying degrees of block is a prerequisite for the production of fibrillation.

The first theory, a modification or elaboration of the earlier views of McWilliam[21] and of Winterberg,[35] has been sponsored by Rothberger and Winterberg.[30, 28] It is variously known as the "tachysystole" or "polytopic" theory, depending upon whether one or several foci are assumed to be responsible for the continued, rapid excitation of the muscle. Closely allied to this explanation are those propounded by Hering[9] and Haberlandt,[7] who suggest that the responsible focus is the A-V node and by Scherf,[32] who postulates that the sino-auricular node may assume a similar rôle.

The second conception is that advocated by Garrey.[6] It is based on the experiments by himself, by Mines,[23, 24] and by the forerunners in the field of "circus motion," Romanes[26] and Mayer.[20] The theory follows the suggestion first made by Mines[24] that this mechanism might be responsible for paroxysmal tachycardia and fibrillation of the heart. Garrey[6] postulates that a provocative stimulus occurs under conditions favorable to the onset of fibrillation, that is, in the presence of factors interfering with the even and coordinated spread of the impulse throughout the heart muscle. In his own words[5] (p. 412): "From the point stimulated the impulses can spread in any and all directions, their progress being limited only by the preexistence or development of localized blocks within the tissue mass. Such blocks divert the impulse into other and more circuitous paths, and the area so blocked off can participate in contraction only when an impulse which has passed to other portions of the ventricle approaches it from another direction; this area thus in turn becomes the center from which the progress of contraction is continued, to be in its turn diverted by other blocks. . . These conditions make possible the propagation of the contraction wave in a series of ringlike circuits of shifting locations and multiple complexity. It is in these 'circus contractions,' determined by the presence of blocks, that we see the essential phenomena of fibrillation." This theory, therefore, does not require that the excitatory impulse should be continuously repeated from the point of origin nor that there should be a single circulating or "mother" wave. The

process, once instituted, is, by this conception, capable of perpetuation even though the auricles should be separated from one another, for a possibility of multiple small secondary "circus movements" is envisaged which may serve as mobile reactivating foci in each large area of auricular muscle.[6]

The third theory is that propounded by Lewis[11] on the basis of researches pursued in his laboratory. The essential postulate of this theory is that in fibrillation, as in flutter, there is a rapidly circulating *single* central or "mother" wave which gives rise to centrifugal or "daughter" waves to the outlying parts of the auricle. Lewis holds that the parent wave may itself be blocked and obliged temporarily to adopt a new and sinuous pathway in a new plane but that it consistently retains its "circus" character, travels usually in a broadly delimited pathway and, if occasionally deviating, invariably returns to its original course which encircles the mouths of the great veins. He states[11] (p. 341): "*A priori* it is possible to conceive of circus movements of many types. We might even assume several circuits, completely or transiently independent of each other, and each controlling for a time material sections of the muscle; we might assume a single circuit wholly erratic in its course, looping widely in and out, sometimes breaking transiently into several circuits. *None of these views would meet the case of fibrillation as it exists clinically.** There is more demonstrable order in the disorder than is consistent with one or other of these mechanisms." It is further held that the oscillations or "f" waves of electrocardiographic indirect leads from clinical cases are a measure of the prevailing rate of the "circus movement" in the auricle. These oscillations have also been studied by Lewis, Drury and Iliescu,[15, 16] who showed that a rotation of the electrical axis of each auricular "cycle" or oscillation through 360 degrees takes place both in auricular flutter and auricular fibrillation in man.

Of the three theories, that of Lewis today claims most adherents. It is particularly attractive, apart from the strong experimental evidence upon which it is based, because it supports a wide measure of clinical experience in linking auricular fibrillation with auricular flutter through an intermediary stage of impure flutter. Its application to cases of persistent auricular fibrillation is less clear, and the theory has been attacked by Rothberger,[28, 29] Garrey,[6] and more recently by Brams and Katz.[2] The latter have published evidence to prove that when the continuity of conduction of the fibrillating auricles is interrupted so as to divide the right auricle from the left both chambers continue to fibrillate. This, as well as certain experiments by Garrey,[6] are held to be unexplainable by the concept of a single central "mother" wave around the mouths of the great veins.

It is precisely because of the still considerable divergence of opinion on this subject that a brief restatement of the essential features of the

*Italics ours.

various theories has been a necessary prelude to the presentation of additional evidence.

Of the entire series of 142 human subjects who have been investigated by the esophageal lead, 21 suffered from auricular fibrillation. Fourteen of these were earlier victims of rheumatic fever; 5 had severe arteriosclerosis and hypertension; and 2 were thyrotoxic. The majority of the cases had demonstrable (and in 5 great) dilatation of the left auricle. In these it was observed that the esophagus was displaced backward and to the right. This finding ensured that an electrode placed in the esophagus would not only be brought into even closer proximity to the surface of the auricle than normally is the case but also would be displaced toward the interauricular zone where a "mother" wave might be expected to have its location.

In the published curves of Lewis[11] (*Fig. 317*, p. 337), taken by direct leads from the exposed auricular surface of dogs in which auricu-

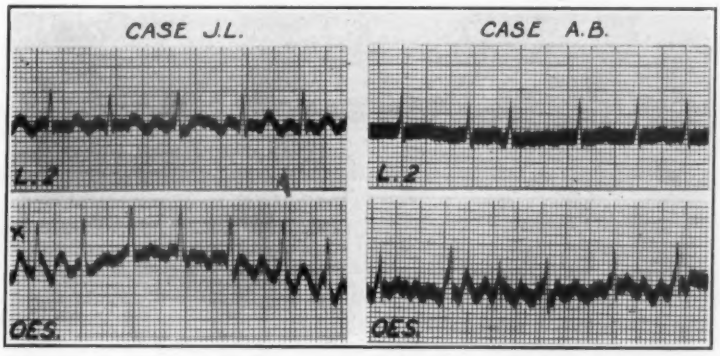

Fig. 17.—Patients J. L. and A. B. Records from two cases of auricular fibrillation. Lead II shown above in each case and esophageal records below.
Case J. L. Auricular fibrillation occurring in hyperthyroidism. The cross marks a doubtful example of intrinsic wave formation.
Case A. B. Auricular fibrillation occurring in rheumatic heart disease.
Standardization in both curves, 1 mv. = 10 mm.

lar fibrillation had been induced, definite intrinsic deflections are recorded. It has also been stated by Lewis[11] (p. 282) and implied by the published chest lead curves of Drury and Iliescu[4] from a human subject that if the electrodes could be brought closer to the surface of the heart of man the recorded "f" waves would be accentuated in amplitude and, presumably, in detailed form. That this is true in auricular flutter has already been demonstrated by esophageal electrograms showing excellent examples of intrinsic deflections. These facts and, in particular, the curves of Drury and Iliescu[4] from precordial leads seem to justify a confident anticipation that the application of the esophageal electrode to cases of clinical auricular fibrillation would yield records illustrating intrinsic deflections. Despite the operation of factors calculated to heighten the sensitivity of the esophageal lead, this expectation has been very rarely fulfilled.

Typical esophageal and conventional records are illustrated in Fig. 17. In only one instance in these curves is there the slightest trace of an intrinsic deflection. If the two cases of hyperthyroidism are excluded, the remaining 19 cases show an entire absence of intrinsic deflections. In all patients as many as seven esophageal records from as many auricular sites have been taken. Some patients (five) have been re-examined on separate occasions. In three subjects postural tests have been employed in an attempt to place the electrode nearer the inter-auricular zone. In 183 separate records of esophageal leads taken from these nineteen patients, there is no instance in which more than a moderate increase in the amplitude of the "f" waves has been observed; the oscillations, though often of considerably greater voltage, have invariably remained slurred and lacking intrinsic deflections.

In the two cases of hyperthyroidism the results were otherwise. Records from one of these patients in whom the irregularity had been present for over three years are shown in Fig. 17 (Case J. L.). The

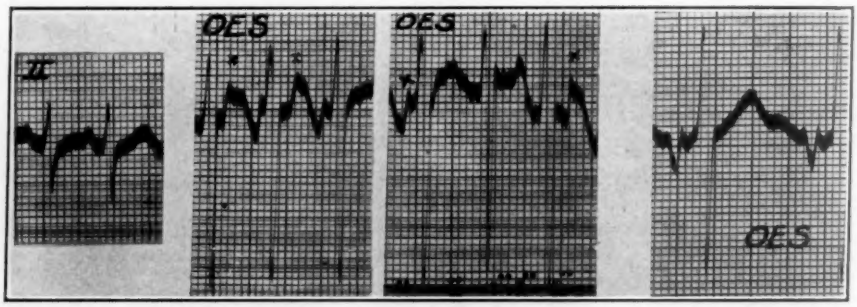

Fig. 18.—Patient M. G., a case of servere hyperthyroidism. The first three curves (Lead II and two esophageal records) were obtained when auricular fibrillation was present. Note the presence of intrinsic deflections as indicated by crosses. The last curve is an esophageal record obtained after spontaneous reversion to normal sinus rhythm following thyroidectomy. Note the deformity of the P-waves in the latter.

second case, a woman aged forty-two years, who had a basal metabolic rate of +71 and a history of auricular fibrillation for three months previous to examination, is of greater interest. The preoperative records of this patient are illustrated in Fig. 18, in which perfectly definite examples of occasionally occurring intrinsic waves are present. The last record of Fig. 18 shows an esophageal electrogram from the same patient obtained when normal sequential rhythm spontaneously appeared following thyroidectomy.

The two cases of auricular fibrillation in hyperthyroidism prove that the method is capable of detecting intrinsic deflections when they occur. Such deflections must represent the activation of a fairly substantial part of the auricular muscle in a locally coordinated manner. The slurred form of the recorded oscillations obtained in cases which show no intrinsic deflections is probably attributable to a fine division of the excitatory wave traveling in areas characterized by local blocks of great complexity.

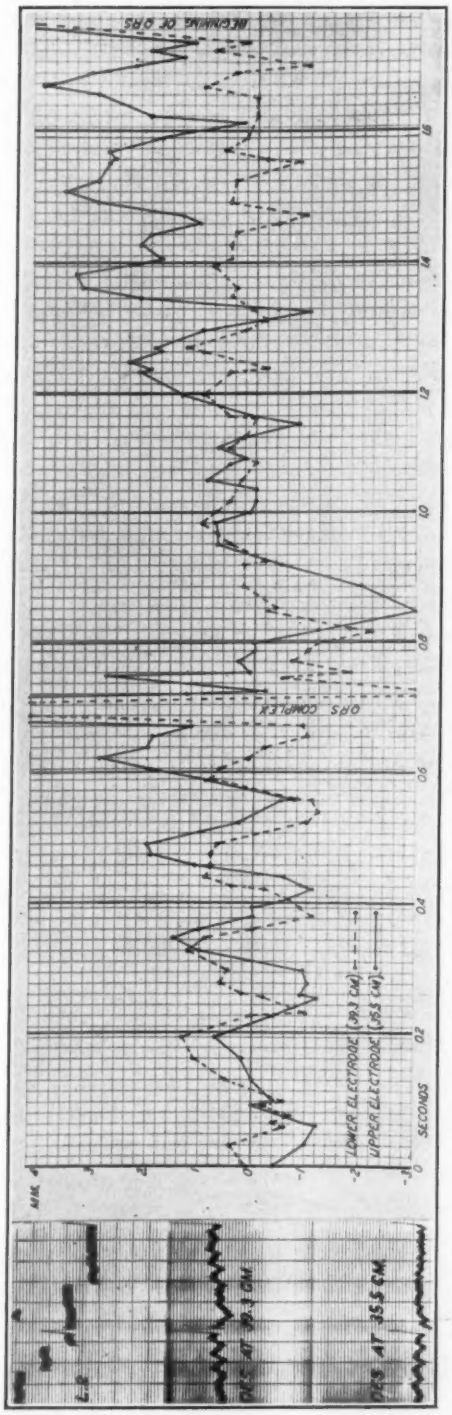

Fig. 19.—Patient C. B. The curves at the left were obtained as described in the text by the simultaneous recording of Lead II and two separate esophageal leads at the depth of 39.3 cm. and 35.5 cm. from the teeth. The latter have been analyzed by the comparator and graphically represented. The abscissae indicate time in seconds, the ordinates height of the deflections in millimeters. (For discussion, see text.)

In the section on flutter it was shown (Fig. 16 and Table I) that evidence of progressive excitation of the tissue in the left auricle underlying the esophagus was elicited. The peculiar time relationships of the intrinsic deflection for the various positions of the electrode were compared with the findings in the P-waves of normal cases, and the results were offered as evidence in support of Lewis'[11] version of the circus movement theory. An experiment was devised to investigate clinical auricular fibrillation along similar lines. An arteriosclerotic man aged sixty-six years, who showed only slight enlargement of the left auricle in the presence of auricular fibrillation, was selected. A double esophageal lead (see Part I, Fig. 5[3]) was passed until each electrode lay behind the left auricle. The electrodes were separated by a distance of 3.8 cm. Each esophageal electrode was attached to a right-arm terminal of a two-stringed Cambridge galvanometer. The left leg served as a site for the remote electrode in each instance. A single-string Hindle galvanometer was attached to the patient to record conventional Lead II. The resistances of all three circuits were balanced to obviate interference. By means of suitable prisms the movements of the three strings were recorded simultaneously.

Typical examples of the curves obtained from the patient under the above conditions are shown in Fig. 19. The esophageal electrograms of the recorded curves illustrated in Fig. 19 have been carefully measured with the comparator and plotted together on the basis of a common isoelectric line. The graph and the curves shown begin at a point 0.34 sec. after the foregoing QRS complex and are certainly free from ventricular effects at the time line marked 0.2 sec. An entire absence of intrinsic deflections is characteristic. The time relationships of the oscillations in the esophageal leads are clearly depicted in the graphical analysis of the curves. In the first part of the curves both electrodes have recorded oscillations of large amplitude lacking a sustained and ordered time relationship. After the QRS complex is written, the electrodes record much grosser differences in the form and occurrence of the "f" waves. The curves from the lower electrode are now finely segmented and of much smaller amplitude than those from the upper. Almost all semblance of order has disappeared, the onset of the smaller waves (lower electrode) occurring now before and now after the beginnings of the larger waves with frequent interpositional wavelets.

DISCUSSION

Similar results to those illustrated in Fig. 19 have been obtained in several records from the same and other patients. The absence of intrinsic deflections might conceivably be explained on the view that the esophageal electrode consistently failed to tap any part of the pathway of the "mother" wave. In view of the findings in flutter it is scarcely conceivable that, if a broader central circulating wave

were present in fibrillation, it would fail to give rise to occasional intrinsic deflections in 183 records from 19 cases. Argued on the basis of Lewis' theory[11] it seems necessary to postulate that at no time did the "mother" wave invade any tissue lying close to the electrodes. On the other hand, the changing character of the waves as illustrated in Fig. 19 could be partly explained on his theory by supposing that the plane of the "mother" wave had wandered farther from the lower electrode in the latter part of the record. But even this does not carry conviction, for it seems clear that any attempt to determine the direction of the electrical axes of such oscillations[15, 16] would be valueless in proving a central circus motion in this clinical case. A much more likely explanation would appear to be that at all of the investigated sites in nineteen cases the oscillations recorded by the esophageal electrode are the resultant of the total electrical potential variations in the areas closest to the electrode. This in turn implies that in these areas *multiple impulses* are traveling and giving rise to electrical vectors which by their sum or subtraction determine the movement of the galvanometric string. It follows that under the circumstances the number of such "f" waves could not be accepted as indicating the rate of circulation of a single "mother" wave.

The experimental work of Lewis[14] (see *Figs. 6-13,* inclusive) has proved that intrinsic deflections are obtainable by direct leads from the fibrillating auricles of dogs and that under these conditions there is strong evidence[11] that a single central circus movement is present. In these animals it is difficult to prevent spontaneous reversion to normal rhythm. In the only case of this series (Fig. 18) in which spontaneous reversion took place, intrinsic deflections have also been observed occurring singly or in a shortly consecutive order. If it were held that the formation of intrinsic deflections is characteristic only of the "mother" wave, then the pathway of the latter must, on this evidence, be considered to be a very devious example of "Umwandlung." Nevertheless, the example is important, for clearly the arguments of Lewis are applicable to this instance. It is quite possible that in this case a single central circus movement is present, that the direction of the electrical axis might be determinable, and that the predominant rate of the larger oscillations might represent the rate of the circulating "mother" wave. The case is one of severe thyrotoxicosis, a condition in which auricular flutter, impure flutter, and auricular fibrillation are quite commonly found. The question naturally arises whether the casual mechanism of auricular fibrillation in thyrotoxicosis, in paroxysmal attacks as well as in successful digitalis therapy in auricular flutter may not be exactly what Lewis postulated. Such cases quite frequently revert spontaneously from auricular fibrillation to normal rhythm. They resemble in this respect the characteristics of auricular

fibrillation artificially produced in experimental animals, but differ entirely from the common clinical examples of the irregularity which tend to persist.

In the present series no trace of an intrinsic deflection has been discovered in any example of *persistent* auricular fibrillation. It seems reasonable, therefore, to suspect that there may be a relationship between a tendency to spontaneous reversion, the presence of a single central circus movement, and the discovery of intrinsic deflections by semidirect leads. The results which have here been reported do not provide decisive evidence, but, when taken in conjunction with the experimental work of Garrey[6] and of Brams and Katz,[2] they are highly suggestive. They urge a reconsideration of the claims of a single "mother" wave as the responsible or enduring mechanism in persistently fibrillating patients. The results of the reported experiment (Fig. 19) are those which would be expected if (in accordance with Garrey's view) the single central wave had disintegrated into secondary, tenuous "circus motions" which serve as multiple, moving, and reactivating foci to the discoordinated muscle areas. Certainly there seems to be no good reason for supposing that this could not occur, and the suggestion is made that, if and when it takes place, the chances for spontaneous reversion to coordinated beating are thereby rendered remote. In other words, it is proposed that this development changes a case which tends spontaneously to revert to normal rhythm into a case in which a state of fibrillation remains obdurately persistent. It is further held that arguments based upon experimental animals which are with difficulty maintained in fibrillation are not strictly applicable to the *majority* of cases of auricular fibrillation as encountered in clinical medicine.

Summary of Section II

The results of applying the esophageal lead in the study of three cases of auricular flutter are illustrated and discussed.

The three most generally accepted views of the mechanism underlying auricular fibrillation are briefly set forth.

The findings obtained in 21 cases of auricular fibrillation in which the esophageal method has been used are illustrated by typical curves and discussed.

A special investigation in a case of auricular fibrillation by means of a double esophageal electrode is described. The findings are analyzed and tentative conclusions are offered as to their significance.

SUMMARY OF PART II

1. The results of employing the esophageal lead in an electrocardiographic study of auricular disorders in 92 human subjects have been recorded, analyzed and discussed.

2. The value of applying the method to patients exhibiting auricular abnormalities has been established.

3. Findings of particular interest have been obtained with reference to auricular arrhythmias (notably auricular tachycardia, auricular flutter, and auricular fibrillation).

GENERAL SUMMARY

1. The results of employing the esophageal lead in one hundred and forty-two human subjects have been analyzed in the light of practical and theoretical considerations. From both points of view, the lead has been proved to be a reliable and valuable electrocardiographic method of the semidirect type.

2. Interpretations of normal and abnormal esophageal curves have been supported by the results of animal experimentation.

3. The conclusions reached, after a study of a wide variety of clinical cardiac abnormalities, have been summarized under the appropriate headings.

4. Suggestions have been made as to the use of the method in clinical research.

In conclusion the author wishes to express his deep indebtedness to Dr. Edward P. Carter for his invaluable aid, advice and encouragement, to Dr. E. Cowles Andrus for his interest and help, and to Miss J. A. Vickers for her technical assistance in the recording and preparation of the electrocardiographic material, all of which have contributed immeasurably to the pursuit of this study. The writer's thanks are also due to the donor of the Bingham Fellowship without whose generous aid this investigation would have been impossible.

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UNUSUAL FEATURES OF TWO CASES OF SINO-AURICULAR BLOCK*

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SINO-AURICULAR block is a rather rare finding in the clinic. For a long time the possibility of its existence was denied by eminent cardiologists (Lewis[1]) because in spite of many investigations (Thorel,[2] etc.) no specific pathway could be found between the sinus node and the auricular musculature. In animals S-A block has been produced by the so-called first Stannius ligature. Joachim[3] even succeeded in observing spontaneous S-A block during an experiment. But for a long time nobody saw this disorder in the mammalian heart, in which the anatomical structure of the sinus node is widely different from that of lower animals.

Finally by analyzing polygraphic curves, Mackenzie[4] and Wenckebach[5] showed clear evidence of the existence of S-A block in man. In addition to complete S-A block, which cannot be recognized electrocardiographically, Wenckebach distinguished two types of partial S-A block, which are analogous to Mobitz's[6] classification of partial A-V block. In Type 2 the P-P interval is practically uniform throughout the record, and after several normal P-QRS complexes one or more auricular waves (with the accompanying ventricular complexes) are dropped out. In this form of irregularity the basal rhythm is not altered, the pause forming a multiple of the P-P distance. In Type 1, the progressive form of S-A block, the P-P interval gradually increases, and after several complexes one or more P-QRS complexes are dropped out. In this form the pause is shorter than a multiple of the P-P distance. The explanation of this form is as follows: Sinus impulses, which of course cannot be seen in the curve, arise rhythmically. The first sinus impulse will be conducted to the auricle in normal time. Conductivity being impaired, the second impulse will reach the tired auricle a little more slowly. Later impulses will require a progressively longer time to reach the auricle. After several such cycles the conducting tissues will be completely exhausted, and the sinus impulse will fail to reach the auricle. Therefore, progressive increase of the P-P distance, followed by longer pauses, will be noticed in spite of normal impulse formation in the sinus node.

Many electrocardiographic records representing S-A block of Type 2 have been published, especially in the American literature, but the more interesting Type 1 is known only by venous curves, typical electrocardiographic records being unknown at present. The most important textbooks of electrocardiography, such as those of Lewis,[1] Clerc,[7]

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Dressler[8] and Weber,[9] show no records of S-A block. Wenckebach and Winterberg,[10] in their atlas, show only one illustration of Type 1 block, published earlier by Edens.[11] Dressler, in his textbook presents only one case observed by Popper and Fischer.

Neither of these two cases is typical, however, for in the records the chief characteristic of Type 1 block, the progressive increase in the P-P distance, is absent. The authors presenting these two examples arrive at their conclusions only indirectly by assuming that in the case of Type 1 block *not the first,* but the *second* P-P interval, must be the shortest, therefore that progressive increase of P-P should begin only after the *second* P-P interval. Venous curves suggest this to be the rule, but the electrocardiographic records are not convincing because in the two cases cited the auricle drops out after each first or second P-P interval, consequently failing to show the law of progressive delay in conductivity for longer periods. Thus the sole assumption for which there are no convincing explanations, that in S-A block of Type 1

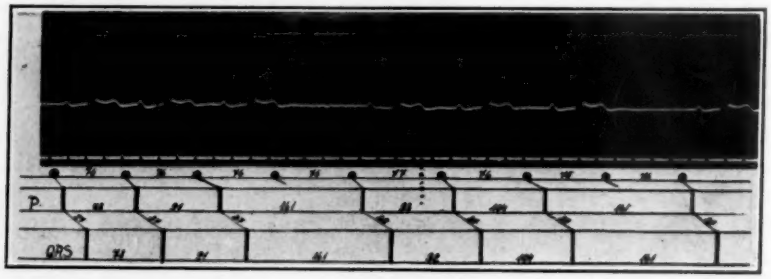

Fig. 1.—The upper line represents the supposed rhythmic formation of excitation in the sinus node (indicated by dots). Next line: gradual increasing of S-A conduction time, with no conduction after the third sinus impulse. P-line auricular waves. Next oblique line: Uniformly prolonged A-V conduction time. QRS line: ventricular contractions.

the second P-P interval is shorter than the first, leads these authors to assume the existence of S-A block of Type 1 in their electrocardiographic curves.

In this paper electrocardiographic records of two patients are presented. These show interesting points concerning both types of block. They are the first published records to show clearly (a) that in S-A block of Type 1 progressive delay in conductivity begins with the first cardiac cycle and persists over a rather long period (7 systoles) and (b) that progressive partial S-A block can coexist with progressive partial A-V block, a fact suggesting convincing evidence as to the mechanism of S-A block.

CASE 1.—G. S., a well-nourished woman, houseworker, thirty-one years old, complained of palpitation which had persisted for four years, increasing in the last three months. There were no other complaints except dysmenorrhea. There was no history of rheumatism or infectious disease; no evidence of arteriosclerosis or of focal infection (teeth, tonsils) could be found. Toxic effects of alcohol, nicotine, and lead could be excluded with certainty. Wassermann reaction and Kahn test were

negative. The blood picture was normal (red cells, 5,000,000; hemoglobin, 100 per cent; white cells, 6,400; differential—band forms, 2 per cent; segmented, 64; eosinophiles, 2; basophiles, 0; monocytes, 6; and lymphocytes 23 per cent). Physical and x-ray examination showed the heart to be of normal size. The sounds were clear and well accentuated, with no murmurs. The blood pressure was 125/70. There were no signs of decompensation. On auscultation and on palpation of the pulse the heart was found to be irregular, with a pause after each second or third beat.

The first record, taken Sept. 19, 1935 (Fig. 1), shows a longer pause not interrupted by P-waves, after each second or third "normal" complex. As sinus arrhythmia, ectopic rhythm, and blocked auricular extrasystoles can be ruled out, sino-

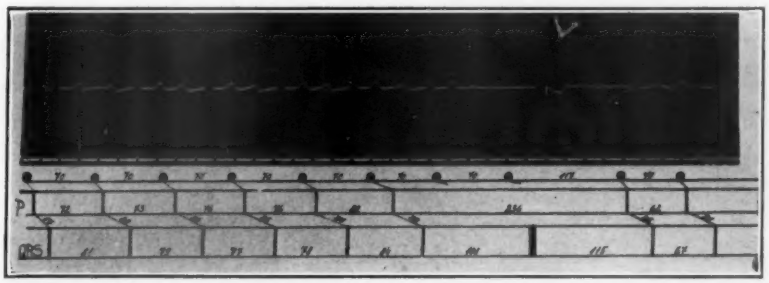

Fig. 2.—The upper line represents the supposed rhythmic formation of excitation in the sinus node (indicated by dots). Next oblique line: gradual increasing of S-A conduction time, with no conduction after the sixth sinus impulse. In the long pause a ventricular escaped beat is to be seen.

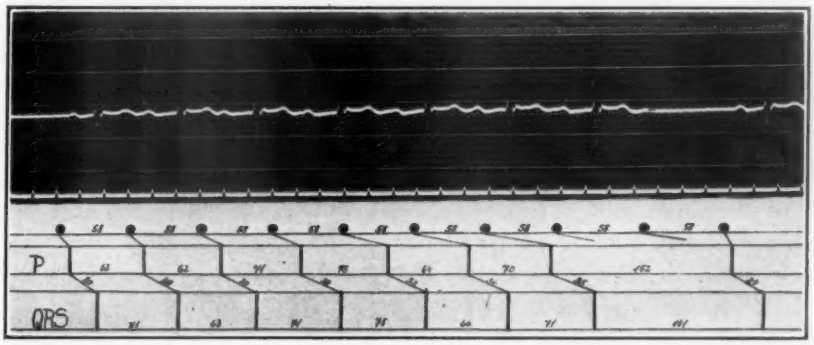

Fig. 3.—See Fig. 2. Dropped beat only after the seventh sinus impulse. No escaped beat. After the long pause the same periodicity begins again.

auricular block remains the only possible explanation. As the P-P intervals are gradually increasing before the pauses, the record is interpreted as belonging to Type 1, which interpretation is supported by later records. The P-R interval is 0.27 sec. (The very low voltage of the standard leads does not permit undisputed analysis of the record.)

The second record (Fig. 2), taken on September 28, shows sino-auricular block of Type 1. An auricular beat is dropped after every sixth complex; the P-P interval increases progressively from 0.72 to 0.82 sec. and the P-R interval increases from 0.17 to 0.39 sec. There are ventricular escaped beats in the long pauses. There is low voltage.*

*Lead II is shown, and the string is standardized so that 2 cm. represent 1mv.

The third record (Fig. 3), taken on October 8, shows a similar condition. After seven cardiac cycles a beat is dropped; the P-P interval increases from 0.62 to 0.70 sec.; and the P-R interval increases from 0.20 to 0.35 sec. There are no escaped beats.

The basal metabolic rate was – 25 per cent and some weeks later was –33 per cent. Menstruation was painful.

As to therapy, epherit decreased the frequency of dropped beats to some extent, but this effect was only transitory. Atropine (0.5 mg. hypodermically) produced the paradox reaction described by Eppinger and Hess[12] with an auricular or nodal ectopic rhythm and a bradycardia of 40 per minute. On giving thyroid tablets (0.10 gm. three times daily) for two weeks, the rhythm became regular for longer periods. When thyroid medication was omitted, the arrhythmia always reappeared but gave place to normal rhythm when the medication was again introduced. The patient now visits the clinic every week or so. She takes thyroid tablets periodically; she has normal sinus rhythm and no complaints.

Discussion of Case 1.—There are three principal points which justify the publication of this case:

1. After reviewing the literature it seems to be the first published case in which longer periods of the progressive form of S-A block are to be seen. From our figures it can be deduced that the generally accepted teaching according to which the first P-P interval must be longer than the second is not a general rule, for in our figures the P-P distance increases gradually from the first cycle to the last one before the pause. This regularity corresponds perfectly to theoretical considerations which gain a strong support from our records. The opposite observation, i.e., that the first P-P interval is longer than the second, appears to us to be exceptional and not in accord with theoretical possibilities.

2. In our case A-V conduction is impaired too. In Fig. 1 it is uniformly prolonged to 0.27 sec. The combination of S-A block of Type 2 (with constant P-P intervals) with uniformly prolonged A-V conduction is well recognized, having been described by Hewlett,[13] Korns,[14] Mackenzie,[4] Rihl,[15] Wallace and Katz,[16] and others, but the coexistence of the *progressive form* (Type 1) of S-A block with the *progressive form* (Wenckebach periodicity) of A-V conduction delay as illustrated in Fig. 2 and 3 has, we believe, not been recognized before. Nevertheless, it is not without importance, for, according to Wenckebach, the second type of heart-block is not surely a disorder of *conductivity,* but rather can be regarded as evidence of disturbed *contractility,* as disease of the musculature and not of the conducting system. In our case, however, the combination of definite defect of conductivity between sinus node and auricle and also a similar defect between auricle and ventricle proves with certainty that we have to do with no circumscribed lesion in some part of the heart musculature but that there is present a systemic disease affecting all conductive pathways. Figures 2 and 3 clearly illustrate the double Wenckebach periodicity in two different parts of the heart, between sinus node and auricle and between auricle and ventricle.

In the long pauses ventricular escaped beats arise and prevent the marked slowing of the pulse which would otherwise result from the coexistence of S-A and A-V conduction defect and which would be likely to cause serious disturbance of the general circulation.

3. All the electrocardiograms of this patient show low voltage. This fact is in accordance with the lowered basal metabolism. This is not a case of marked myxedema, for all skin symptoms and nervous signs are missing. Low basal metabolism and dysmenorrhea can more easily be referred to abnormal function of the hypophysis or to hypofunction of the adrenals, or to a combination of the two. It is well known that the adrenal cortex influences the gonads, and medullar hypofunction causes hypoadrenalemia, which leads to decreased sympathetic and increased vagus tone and which in turn may cause disturbance of conductivity in the heart.

According to most writers S-A block is rarely caused by anatomical lesions; more often—perhaps always—it is the expression of nervous or toxic influences. This interpretation must be extended to include hormonal disorders too.

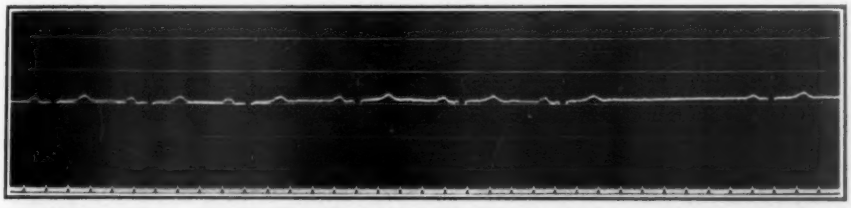

Fig. 4.—S-A block of Type 2. Constant P-P distances. Dropped beat after each sixth sinus impulse.

Nervous and endocrine troubles are always correlated with each other. Hormonal products influence the vagi and the accelerans, whose endings in turn later produce hormonal substances of cholinlike and adrenalinlike nature (Loewi,[17] Beznák[18]). Accordingly, the mechanism by which the two opposed representatives of the autonomic nervous system influences the underlying physiological units may be described as humoral (molecular) rather than neurophysical.

In this case digital compression of the vagi (carotid) and also holding the breath failed to have any effect on the arrhythmia. Emotion (fright) or bodily work (increased sympathetic tonus) suppressed the arrhythmia for some minutes, while epherit caused a diminished tendency to arrhythmia for longer periods and thyroid tablets were successful in maintaining regular rhythm as long as the medication was continued. This supports the view that hormonal disorders, disturbed neurohormonal equilibrium, were responsible for this rare form of arrhythmia.

A few months later we had the opportunity of observing another case of partial S-A block (Fig. 4). This record merits little attention for

it represents the common form (Type 2) with constant P-P intervals. Nevertheless, we consider that this case also is worthy of brief consideration because of the etiological factors, a cerebral tumor probably being responsible for the cardiac irregularity.

CASE 2.—The patient, a housewife, forty-two years old, appeared pale, undernourished, and nervous. She had no complaints referable to the heart. She had terrific headaches, visual disturbances, and serious psychic disorders, at times being completely disoriented.

On physical examination the heart was normal in size, the sounds were clear, and there was no hypertension or signs of decompensation. Cardiac irregularity was present, with regular intermittence after each sixth systole. The Babinsky phenomenon was present on the left side. Apart from this there were no other abnormal neurological findings in the motor or sensory field or in the reflexes. Ophthalmological examination, however, revealed choked disks in both eyes. On performing lumbar puncture cerebrospinal fluid appeared under high pressure. The height could not be determined because of the patient's restlessness. The cell count and all tests (Nonne-Appelt, Pandy, Weichbrodt, and Wassermann reactions, Kahn test, and colloidal gold curve) were normal. The next day encephalography was undertaken, but unfortunately the patient died within a few minutes after air was introduced. Permission for necropsy was refused by the family.

Discussion of Case 2.—In spite of the dearth of local and general signs and symptoms, we were inclined to assume that the patient had a brain tumor in the posterior fossa, because of the headaches radiating to the back of the neck, the symmetrical choked disks, the high intralumbar pressure, and the hypothetic vagus sign, S-A block. This latter assumption was strongly supported by the striking fact that after lumbar puncture the arrhythmia ceased promptly and regular rhythm persisted for some hours. Thus, while the presence of brain tumor could not be proved with certainty, the evidence (especially in the absence of other cardiac, toxic, or hormonal disorders) of (1) increased intracranial pressure, (2) cessation of cardiac arrhythmia after lumbar puncture, and (3) death of the patient when intracranial pressure was increased by the introduction of air, strongly support the view that elevated intracranial pressure was the cause of increased vagal tone which resulted in the S-A conduction defect and in the final fatal issue.

CONCLUSION

It has been shown that in the first case hormonal disorders influenced in a qualitatively identical manner the A-V conduction (i.e., genetic system) and the S-A conduction (common musculature). It seems unlikely that the same noxa should influence in the same way two tissue elements differing so widely from one another as do the genetic system and the common musculature. Lewis' interpretation seems to us to be more probable, namely that S-A block has its seat not *between* the sinus node and the auricular musculature, but *in* the sinus node itself, i.e., on its borders, from where excitation radiates synchronously in every direction to neighboring parts of the auricular musculature. Thus it

can be understood that a toxic agent traumatizes in the same manner two elements of the heart with different localization but with identical histological structure, the sinus node and the genetic system, which apparently are characterized by similar susceptibility toward extrinsic influences.

The second case, on the other hand, clearly illustrates the rôle played by purely mechanical factors, such as elevated intracranial pressure, in governing the action of the extracardiac nerves. Thus etiological factors, differing so widely from one another as do chemical (toxic or hormonal) and physical (nervous) disorders in the organism, can both lead to the same pathological process in the heart by way of the cardiac nerves. It matters not whether we consider the second type of heart-block as the result of conduction or of contraction disturbance, for the vagi act in the same manner upon conductivity and contractility.

SUMMARY

Two cases of sino-auricular block are presented. The first represents the rare form, the so-called Type 1, with progressively increasing conduction delay between the sinus node and auricular musculature, associated with progressively increasing A-V conduction delay. This trouble is ascribed to hormonal disorder, and the mechanism of S-A block is discussed.

The second case, in all probability, was caused by brain tumor, elevated intracranial pressure with consequent increased vagal tone causing S-A block of the so-called Type 2.

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ELECTROCARDIOGRAPHIC CHANGES IN HYPERPARATHYROIDISM*

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ALTERATIONS in the electrocardiogram have been shown to occur in the hypocalcemia of tetany, but relatively few clinical observations have been made in the hypercalcemia of hyperparathyroidism.

Hecht[1] and Morgenstern[2] early called attention to the small QRS complexes and the prominent T-waves occurring in the electrocardiograms of patients with tetany. In addition to these findings, Doxiades[3] noted shortening of both the P-R and the QRS intervals. These changes were considered characteristic of hypocalcemia, but more recent reports (Salvadei and Pasoli,[4] and Marzahn[5]) indicate that such changes occur consistently in the electrocardiograms of relatively few patients. Unfortunately but little attention has been paid to the level of the calcium in the blood at the time the electrocardiographic studies were made.

Carter and Andrus[6] were the first to call attention to the prolongation of "electrical systole," or the Q-T interval, in hypocalcemia. This important observation was confirmed by White and Mudd,[7] and more recently by Marzahn.[5] Marzahn laid particular emphasis on the lengthened isoelectric period between the S-wave and the onset of the T-wave, and considered this to represent a tendency of the cardiac muscle to a tetanic state.

Numerous electrocardiographic studies have been made on animals following the intravenous injection of calcium chloride or the administration of parathyroid extract. These studies have been summarized by Berliner[8] and will not be reviewed in detail here. Following the administration to dogs of sufficient parathyroid extract to raise the level of calcium in the serum to 16 to 25 mg. per cent, Gold and Edwards[9] found that premature beats, shifts of the auricular pacemaker, alterations in the T-waves, and varying degrees of impairment of conduction occurred.

Segall and White[10] have reported a series of electrocardiographic studies of human subjects following the administration of calcium. In one patient no electrocardiographic changes occurred after the intravenous injection over a period of 15 minutes of 75 c.c. of 2 per cent calcium chloride solution. Following the daily ingestion of 15 to 24 gm. of calcium chloride for six days, inconsistent electrocardiographic changes appeared in eight of the eleven patients studied. In only one patient was consistent prolongation of the P-R interval noted. However,

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determinations of the concentration of calcium in the serum showed no alteration following the ingestion of such amounts of calcium in the one patient on whom such a determination was made. Measurements of the Q-T interval were not made.

Fujimori[11] has found consistent alterations in the electrocardiograms of fifteen patients following the intravenous administration over a period of two minutes of 20 to 30 c.c. of 3 per cent calcium chloride solution. The Q-T interval* was shortened in all instances. In ten of the patients the P-R interval was appreciably lengthened. Decreases in the heights of the P-waves, QRS complexes and T-waves occurred consistently.

TABLE I

Measurements from electrocardiograms of two patients, before and after operation, with hyperparathyroidism. Both patients show a relatively short Q-T interval before operation, which became longer following surgery. The first patient shows a prolonged P-R interval before operation.

	DATE	R-R INTERVAL* (SEC.)	P-R INTERVAL* (SEC.)	Q-T INTERVAL* (SEC.)	K $\frac{\text{(Q-T INT.)}}{\sqrt{\text{R-R INT.}}}$	SERUM CALCIUM (MG. PER 100 C.C.)
Case 1	Jan. 23, 1934	0.66	0.23	0.30	0.371	19.2
V. F., a seventeen-year-old girl	Jan. 31, 1934	Removal of adenoma of parathyroid gland				
	Feb. 5, 1934	0.87	0.15	0.36	0.386	9.6
	Feb. 9, 1934	0.72	0.12	0.35	0.414	9.2
	Mar. 26, 1934	0.87	0.12	0.40	0.428	9.4
	May 15, 1935	0.80	0.14	0.36	0.407	10.1
Case 2	Mar. 2, 1934	1.12	0.17	0.33	0.312	17.5
J. F., a twenty-three-year-old man	Mar. 19, 1934	Removal of adenoma of parathyroid gland				
	Mar. 24, 1934	1.03	0.17	0.36	0.355	10.0

*Average of four consecutive measurements.

Ballin[12] has published the electrocardiograms taken before and after operation of a patient with hyperparathyroidism. Attention was called to the short S-T interval before operation, which lengthened following surgical removal of an adenoma of the parathyroid. Ballin suggested that this shortened S-T interval might provide an accurate clinical sign for the diagnosis of hyperparathyroidism, supplementing the usual determinations of serum calcium and measurements of chronaxie in patients with hyperparathyroidism.

In a further attempt to evaluate the changes of the electrocardiogram in hyperparathyroidism, serial tracings were made of two patients before and after the surgical removal of an adenoma of the

*Measurements of the Q-T intervals were not corrected for changes in the cardiac rate, which has been shown to influence greatly the Q-T interval. However, when such corrections are made, the Q-T interval is found to be shortened an average of 20 per cent in the fifteen patients studied.

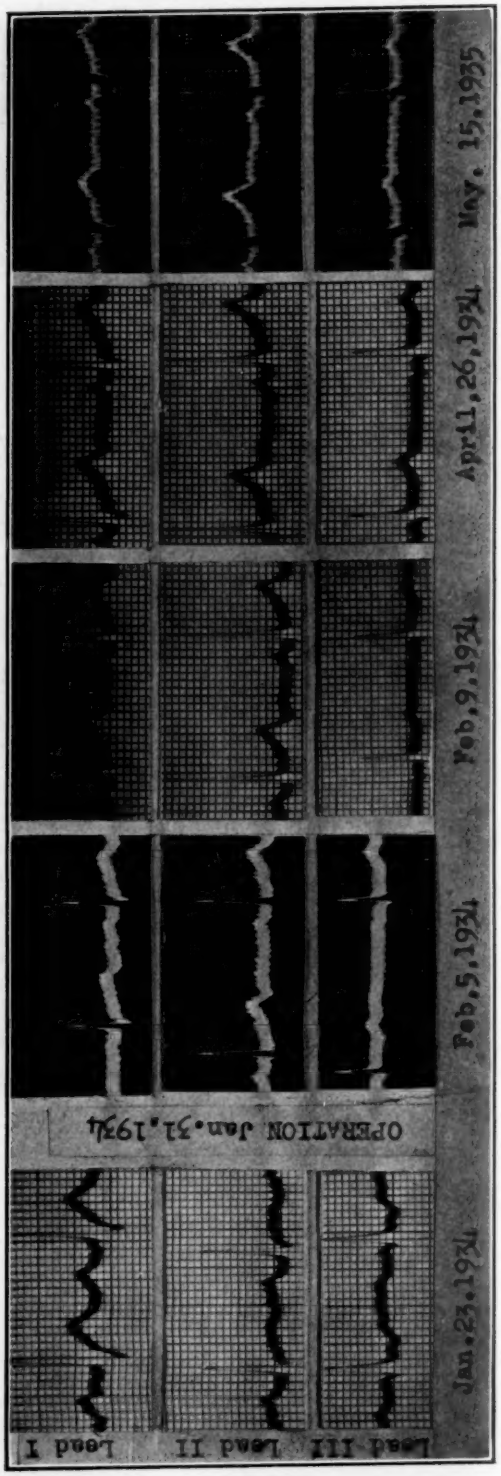

Fig. 1.—Serial electrocardiograms of the first patient (Case 1) before and after surgical removal of a parathyroid adenoma. Note progressive changes in T-waves following operation. Interval between time-marker lines equals 0.04 sec.

parathyroid gland. Both patients had osteitis fibrosa cystica and other findings typical of hyperparathyroidism. As the case reports of these patients are to be presented in a separate paper[13] on hyperparathyroidism, the clinical details will be omitted here.

ELECTROCARDIOGRAPHIC STUDIES

The electrocardiograms of these two patients, brother and sister, before and after operation, are shown in Figs. 1 and 2. The time relationships, together with determinations of the calcium in the serum, are shown in Table I. The column of figures under the heading, *K*, needs explanation. Bazett[14] and Cheer and Li[15] have shown that the Q-T interval is proportional to the square root of the pulse-period or the

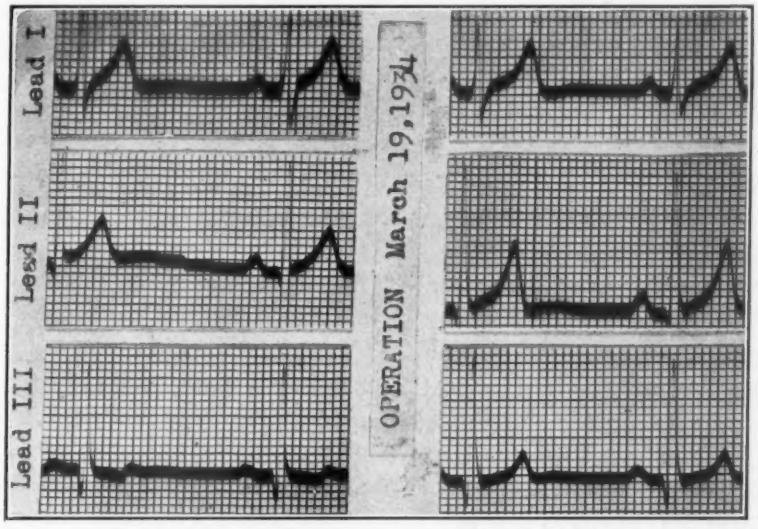

Fig. 2.—Electrocardiograms of the second patient (Case 2) before and after surgical removal of a parathyroid adenoma. Interval between time-marker lines equals 0.04 sec.

R-R interval. Thus, values for K were obtained from the equation $K = \frac{\text{Q-T interval (sec.)}}{\sqrt{\text{R-R interval (sec.)}}}$. Bazett found in males that $K = 0.368 \pm 0.025$, and in females that $K = 0.399 \pm 0.040$. In Chinese men, Cheer and Li found that $K = 0.374 \pm 0.0012$; and in Chinese women, $K = 0.388 \pm 0.0021$.

Several noteworthy changes may be seen in the electrocardiograms of our first patient (Case 1), in whom the serum calcium was almost twice the normal amount. Before operation the auriculoventricular conduction time was abnormally prolonged; the QRS complexes were slightly slurred; the T-waves were abnormally low in Lead II; and the Q-T interval was shortened. Following operation, these deviations from the normal tended to disappear. Within five days the delayed auriculo-

ventricular conduction time and the slurring of the QRS complexes had disappeared; the T-waves in Lead II had become more prominent; the T-waves in Lead III were upright (formerly diphasic), but the T-waves in Lead I were less in amplitude than before. Minor changes in the T-waves continued to occur for several weeks, and the Q-T interval gradually became more prolonged.

Less pronounced changes may be seen in the electrocardiograms of the second patient (Case 2). Before operation the only abnormality was a short S-T interval. Following operation the T-waves became more prominent, and the Q-T interval became somewhat longer. No appreciable changes in the P-R interval or QRS complexes occurred.

It is of interest that the abnormal auriculoventricular and ventricular conduction, seen in Case 1, became normal soon after operation, whereas alterations in the Q-T interval and T-waves continued to occur for some time, although the calcium content of the serum had returned to a normal level.

COMMENT

The changes in auriculoventricular conduction time observed in the preoperative electrocardiogram of Case 1 resemble those found experimentally in dogs given parathyroid extract and those found by Fujimori in human subjects following the intravenous administration of calcium chloride.

Our studies, together with those of Ballin and Fujimori, confirm, as far as hyperparathyroidism and hypercalcemia are concerned, the observations of Carter and Andrus concerning the relationship of the Q-T interval to the calcium content of the serum.

Although shortening of the Q-T interval occurs consistently, it is doubtful if this sign is of much clinical value in the diagnosis of hyperparathyroidism, as the range of the Q-T intervals herein reported fall within the normal limits given by White and Mudd. If the formula of Bazett is used, the deviations from the normal appear more striking, but we doubt whether much significance can be attached to them.

SUMMARY

Serial electrocardiograms on two patients with hyperparathyroidism are reported, which showed shortened Q-T intervals (electrical systole) before operation. Following the removal of an adenoma of the parathyroid, the Q-T interval became longer in the electrocardiograms of each patient. Before operation one patient showed delayed auriculoventricular conduction and slurred ventricular complexes.

It is concluded that the shortening of the Q-T interval is not of sufficient degree to be of value in the clinical diagnosis of hyperparathyroidism.

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Department of Clinical Reports

CARDIAC HYPERTROPHY IN A CASE OF COOLEY'S ANEMIA*

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ANEMIA, experimental or clinical, has but rarely appeared and has been inadequately stressed in the literature as a sole cause of cardiac hypertrophy. In a survey of the causes of cardiac hypertrophy we had occasion to study the heart of a patient in whom at necropsy no causative factor for hypertrophy other than anemia could be found. The case was that of a nine-year-old boy with Cooley's anemia. We were interested in an attempt to derive the underlying mechanism responsible for cardiac hypertrophy in this case.

In the more recent literature, Whipple and Bradford[1] reported two instances of racial anemia with bone and pigment disturbances in two children, a brother and sister, which were similar to our case. The heart of their first patient, a child aged two years, weighed 155 gm. at necropsy and showed typical fatty degeneration. No mention was made of cardiac hypertrophy, and the muscle cells were regarded as normal, though the heart weight was more than double the normal for the child's age. In their second patient the heart was reported as enlarged to the left with a soft systolic murmur present. Necropsy, however, was not performed on this case.

Goldstein and Boas[2] reported diastolic murmurs and cardiac enlargement due to dilatation in anemia, and in one instance, unquestionable hypertrophy. Ball[3] reported cardiac enlargement in pernicious anemia. He had no necropsies, and it cannot be stated whether he was dealing with hypertrophy or with dilatation alone. Daniels and Burright[4] produced experimental anemia in rats by bleeding and observed definite hypertrophy of the muscle fibers of the heart. The weight of the desiccated specimen was found increased in comparison with the weight of the heart of a corresponding normal animal.

REPORT OF CASE

A nine-year-old boy was admitted to the hospital with a history of anemia of lifelong duration. The father and the mother were both Italians, living and well, and there were a brother eighteen years old, and a sister seventeen years old, also living and well. The patient had had measles at five years. Tonsillectomy and adenoidectomy had been performed two and one-half years before admission. At the time of operation an enlarged spleen was found. He was pale all his life. Occasionally he had complained of dyspnea after immoderate exertion and fatigue on ordinary exertion. Two days before admission, he developed pain in the left ear and the following day, a discharge from the ear.

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Examination showed a mentally retarded boy with mongoloid facies, slanting eyes with small palpebral fissures, a sallow, *café-au-lait* color of the skin, bulging of the midportion of the frontal bone, and a saddle nose. There was a high arched narrow palate, and the chest was rachitic. The cervical vessels showed marked pulsations. A systolic thrill was felt over the right common carotid and subclavian vessels. The apex beat was in the fourth interspace just beyond the midclavicular line, and the heart was regarded as slightly enlarged. A soft blowing systolic murmur was heard over the apex, and a rough systolic murmur was present over the aortic region. The apical first sound was reduplicated. The abdomen was prominent. The lungs were clear. The liver was felt five fingerbreadths below the costal margin in the midclavicular line, the spleen, six fingerbreadths below the costal margin. Blood pressure was 104/52 on the right arm, and 88/52 on the left arm.

X-ray examination of the chest showed fairly marked dilatation of the heart. Electrocardiogram showed low voltage.

The blood count on admission was: hemoglobin, 30 per cent; red blood cells, 2.2 millions; white blood cells, 13,800. The differential count was, staff cells, 20 per cent; segmented cells, 54 per cent; small lymphocytes, 25 per cent; mononuclear cells, 1 per cent. Poikilocyotsis, anisocytosis, and macrocytosis were present.

Radiographic study of the skeletal system showed the bone changes typical of hemoblastic anemia as given by Cooley.[5]

X-ray films of the mastoids showed cloudiness of the mastoid cells.

Clinical Course.—While he was in the hospital the hemoglobin level fell to 25 per cent and the number of red cells to 1.2 millions. He was transfused repeatedly and after the third transfusion developed a temperature of 104° F. The boy was discharged after a period of ten months, only to be readmitted four months later. At this time there was slight clubbing of the fingers and toes. The heart was enlarged, the rate rapid, and gallop rhythm was present. The liver edge was felt five fingerbreadths below the costal margin; the spleen was at the ilium; its anterior surface in the loins. A purpuric spot was present on the left shin. Blood count showed: hemoglobin 25 per cent; red cells 0.97 million; white cells 4,800. Serum albumin was 3.28 per cent and, serum globulin, 1.78 per cent. After a transfusion of 250 c.c. of blood, the red cell count increased to 1.46 millions. Shortly after another transfusion the temperature rose to 105.4° F., heart action and respiration became rapid, and he expired shortly thereafter.

Necropsy.—(Only the pertinent findings are reported.) There were 25 c.c. of fluid in the peritoneum. The spleen was considerably increased in size and extended in an oblique line from left costal margin and 2 in. below the umbilicus. The lower margin of the right lobe of the liver extended to the anterior superior iliac spine on the right side; the left lobe occupied the epigastrium, extending below to the umbilicus and above to the left parasternal line, meeting the spleen. The diaphragm was at the fourth intercostal space at both sides.

Heart: Measurements: weight, 200 gm.; aortic ring, 5 cm.; mitral ring, 8.5 cm.; pulmonic ring, 6 cm.; tricuspid ring, 9 cm.; left ventricular wall, 15 mm.; right ventricular wall, 4-5 mm. (The average heart weight for a nine-year-old child is 108 gm.) The epicardial fat was slightly icteric. The organ was moderately hypertrophied. The left ventricle, which usually forms not more than one third of the anterior surface, in this instance formed half of the anterior surface and the entire apex. The myocardium was pale red and flabby. The right auricle was moderately dilated but not hypertrophied, and the trabeculae carneae were flattened. The right ventricle was moderately dilated and hypertrophied. Both inflow and outflow tracts of the right ventricle were increased in length, particularly the latter. The pulmonic conus was slightly dilated. The left auricle was moderately dilated and slightly hypertrophied. The left ventricle was considerably hypertrophied and moderately

dilated, with considerable tigering of subendocardium. The leaflets were slightly icteric, but otherwise showed no abnormalities. The coronary arteries, sinuses, and veins were normal.

Microscopic Findings of Heart: Cloudy swelling and fragmentation of fibers. Cross-striations indistinct. Moderate amount of perivascular fibrosis. Muscle fibers hypertrophied. Nuclei hypertrophied. Lymphocytes and large mononuclear cells in interstitial tissue, usually where degeneration was most marked. A few of the nuclei gave faintly positive reaction for iron.

Fig. 1.—Photomicrograph, high power, showing cardiac hypertrophy.

Pulmonary arteries, veins, and bronchi were normal.

The liver, the spleen, and the skeletal system showed the findings common to cases of advanced hemoblastic anemia.

DISCUSSION

It is interesting to review some of the known physiological facts pertaining to cardiac hypertrophy and to inquire whether these facts furnish an explanation for cardiac hypertrophy in our case.

Frank,[6] supported by Straub[7] and by Wiggers,[8] held that the force of contraction of a muscle was dependent upon the initial tension to which it is subjected before contraction. Starling and his associates,[9, 10] however, contended that while, in general, initial fiber tension corresponded to initial fiber length, the efficiency of fiber contraction was determined solely by initial fiber length.

The mechanism whereby the heart does more work has been shown to be the same both in the normal and in the abnormal heart. Up to a certain point, increased fiber length is associated with a rise in intraventricular pressure and in the height of the isometric contraction curve. By increase of volume the normal heart, as shown by Starling and Visscher,[11] is capable of a wide range of augmented cardiac output and efficiency. With removal of the demand for increased work, the fiber resumes its normal size. However, when the heart has for a long time worked against increased resistance or heightened venous inflow, fatigue and a loss of muscle tone set in. Greater fiber stretching is then required to produce relatively small rises in intraventricular tension. With the persistence of fatigue, despite increasing diastole, both the tension and the isometric contraction curve actually fall.

The diseased heart in its response to work corresponds to the working of the nondiseased heart in fatigue, in that small increases of work require relatively large increments in fiber length. Increased fiber length, which in the normal heart is transitory only, in the diseased heart is usually chronic since cardiac enlargement is common in heart disease. This long-standing increased fiber length appears to be the stimulus in the diseased heart for muscular hypertrophy. The persistence of augmented fiber length results sooner or later, however, in dilatation from inadequate nutrition and insufficient oxygenation. Dilatation, if persistent, leads in turn to additional hypertrophy from increased diastolic stretching. A cycle of dilatation producing hypertrophy may repeat itself for a long time. Eventually, for some unknown reason in the metabolism of muscle, dilatation ceases to produce the stimulus for additional hypertrophy.

Both cardiac hypertrophy and dilatation have been observed experimentally in anemia. In our case long-standing severe anemia was present. Increase in volume, corresponding to increased fiber length, was known to exist clinically. Necropsy revealed also marked cardiac hypertrophy. In the absence of any other demonstrable factor, it seems reasonable to suspect that long-standing increased fiber length was the physiological stimulus for the cardiac hypertrophy observed. It is likely that the hypertrophy following dilatation resulted in maintaining the efficiency of the heart. With the persistence of severe anemia and anoxemia, however, the functional factors responsible for additional dilatation were present and produced even greater hypertrophy.

Decreasing oxygen saturation is associated with progressive cardiac dilatation. Dilatation increases the demand of the heart for oxygen. In our case, though the demand of the heart for oxygen was increased by dilatation, the severe anemia with diminished hemoglobin and the correspondingly reduced oxygen-carrying capacity may have led to a primary loss of contractility from inadequate oxygenation.*

Hypertrophy produced a mechanical disadvantage since the blood supply was distributed over a relatively larger area. Oxygen absorption is known to be greater at slow than at fast pulse rates, and Harrison and his coworkers[15] have called attention to the fact that while the heart muscle of patients with heart disease is usually thicker than normal, the pulse rate is usually not correspondingly slower. Hypertrophy evidently may also be a contributory factor in producing a primary loss of contractility from nutritional insufficiency.

The occurrence of cardiac dilatation in severe anemia is well known. With this dilatation, increased fiber length or fiber tension, or both, are of necessity present and constitute the prime factors responsible for cardiac hypertrophy. Nevertheless, the development of cardiac hypertrophy is a rare occurrence in severe anemia. In other conditions, notably essential hypertension, particularly in women, and in chronic congestive failure due to arteriosclerotic heart disease, long-standing increased diastolic length and tension may be assumed. Similarly, in a considerable number of these cases, too, cardiac hypertrophy does not develop. Evidently in addition to long-standing increased diastolic length, there must be some other factor in the absence of which cardiac hypertrophy does not develop in a considerable percentage of cases of chronic congestive failure and in most cases of severe anemia.

SUMMARY

A case of severe anemia associated with cardiac hypertrophy is reported. The physiological factors responsible for cardiac hypertrophy are briefly discussed. An attempt is made to explain the cardiac hypertrophy in this case from a physiological point of view.

Cardiac hypertrophy is rare in anemia. Since dilatation is usually present in severe anemia and increased initial length may therefore be assumed, some factor other than chronically increased initial length must be present for cardiac hypertrophy to develop.

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*It is interesting to note that anoxemia has been looked upon in the human heart as the underlying cause of angina pectoris. Herrick[12], Coombs[13], as well as Evans[14], were of the opinion that cardiac pain in patients with pernicious anemia was out of proportion to cardiac sclerosis and considered anemia as a factor in the production of cardiac pain. The case of Goldstein and Boas[2] had not only anginal episodes, but cardiac hypertrophy as well with severe anemia.

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WIDELY PATENT FORAMEN OVALE*

Case Report With Discussion of Diagnosis

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COMPLETE anatomical closure of the foramen ovale, in the majority of cases, does not occur until the second postnatal year and in many instances it is delayed much beyond this period (Patten[8]). The general incidence of the probe-patent foramen ovale in individuals twenty years of age or over is approximately 23 per cent (Seib[10]) and can hardly be considered abnormal. A widely patent foramen ovale, however, is a rare congenital anomaly which gives rise to characteristic cardiovascular malformations. The embryological and the pathological features of auricular septal defects have been described in detail by Abbott.[1]

Roesler,[9] in an extensive review of the literature, found 62 cases with interatrial septal defects of 1 cm. or more. He gives a very complete summary and discussion of the clinical features, the pathological physiology, and the laboratory findings, and points out the following: (1) the average duration of life is thirty-six years; (2) three-quarters of the cases are complicated by other valvular lesions, the majority of which are mitral; (3) none is complicated by endocarditis; (4) all the hearts are large, and some are enormous, even in the absence of a valvular lesion, and this enlargement is due entirely, or almost entirely, to a right-sided dilatation which exceeds hypertrophy in a disproportionate degree; (5) the size of the heart is influenced by the size of the defect; (6) auricular fibrillation is common, thus distinguishing it from all other congenital cardiovascular malformations; (7) the five cases with electrocardiographic tracings all show definite right axis deviation, which, however, is marked in only one case.

Assmann[4] was the first to describe the characteristic roentgenological findings of a small aortic knob, prominent pulmonary conus, wide hilar vessels, and an enlarged, globular heart. McGinn and White[7] have summarized twenty-four cases in interauricular septal defect associated with mitral disease (Lutembacher's[6] disease). Similar cases have been reported.[1, 2, 3, 5]

The purpose of this presentation is to report a case of widely patent foramen ovale which illustrates the clinical, roentgenological and electrocardiographic peculiarities of this congenital defect.

REPORT OF CASE

I. G., a seventy-seven-year-old Hungarian born, white female, was admitted to the First Medical Division of Bellevue Hospital on the service of Dr. I. O. Woodruff

*From the First Columbia Medical Division, Bellevue Hospital.

on Aug. 21, 1935, complaining of dyspnea, orthopnea, and substernal pain of six weeks' duration. The history was not entirely satisfactory because of language difficulty. The present illness started six weeks before admission with attacks of sharp, stabbing precordial pain which did not radiate and which was accompanied by dyspnea and orthopnea. Such episodes occurred with the patient at rest or very often were incited by exertion. Two weeks later, she first observed edema of the

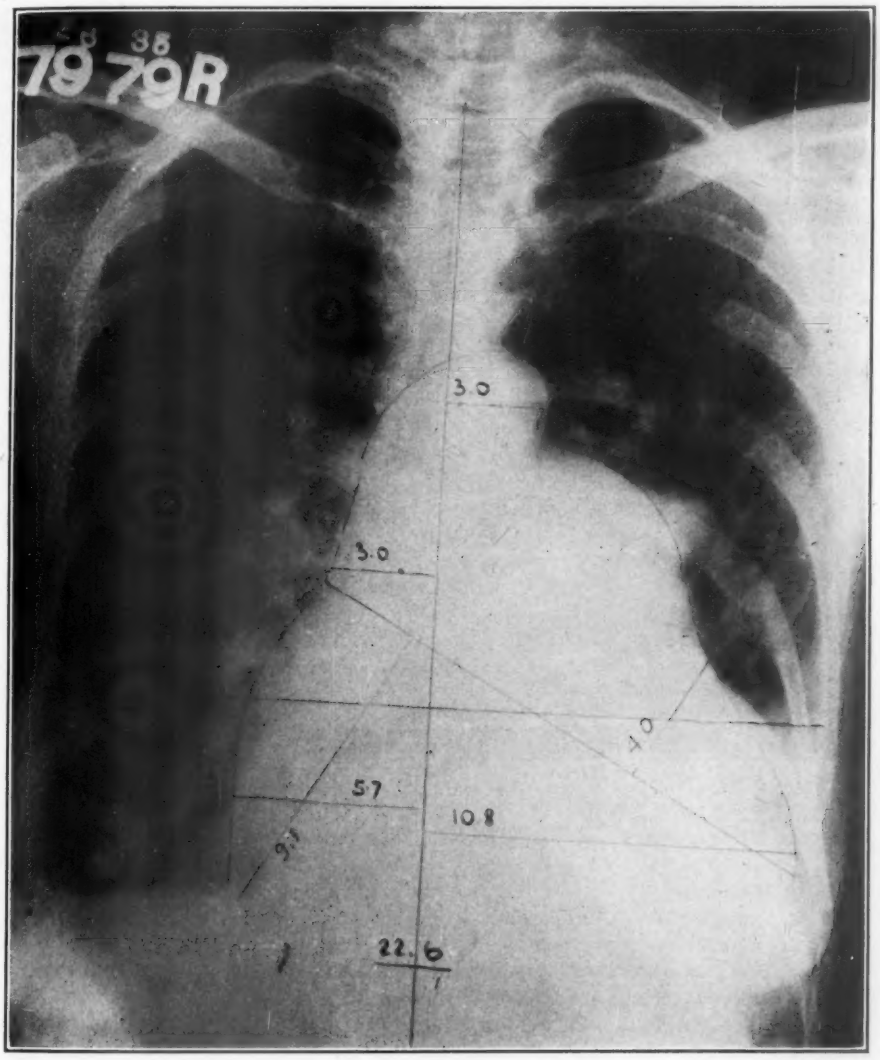

Fig. 1.—The upper half of the left cardiac border is formed by a large rounded pulmonary conus which is sharply offset from the calcified aortic knob superiorly, and from the left ventricle inferiorly. There are congestion and fibrosis at both hilar areas, which extends into bases. The cardiac apex is obscured. The aorta is within normal limits despite the presence of hypertension.

ankles which was progressive up to the time of her admission. The review of systems, past history, and family history was noncontributory.

The temperature was 99.2° F., the pulse 98, respirations 30, and blood pressure 140/110-100.

On admission the patient was noted as a small, poorly nourished and developed, old white female complaining bitterly of precordial pain. She was dyspneic, orthopneic, and cyanotic; noisy and unintelligent. The pupils were equal and reacted to light and in accommodation. Fundi showed advanced sclerotic changes. The mucous membranes were pale and cyanotic. Hearing was unimpaired. There was complete edentia. The lymphatic system was negative. The neck veins were slightly distended. The right breast was fuller and larger than the left, but no masses were felt. Resonance throughout both lungs was unimpaired. Many moist râles were heard over both bases. The apical impulse was palpable in the fifth space at the anterior axillary line. Conus dullness was definitely and markedly widened. A systolic thrill was easily palpable over the pulmonic area in the second interspace to the left of the sternum. The second pulmonic sound was accentuated and greater than the second aortic sound. A loud, rough systolic murmur was present over the pulmonic area. The second aortic sound and a soft systolic blow could be heard over the carotid arteries in the neck. A blowing systolic murmur of moderate intensity

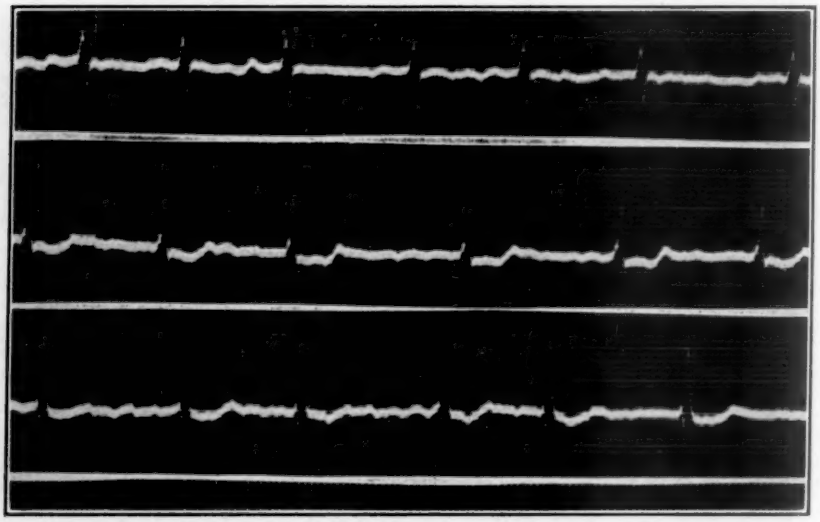

Fig. 2.—Auricular fibrillation with right axis deviation is present. The auricular oscillations are fairly coarse. The ventricular rate averages 75 per minute. The QRS interval is 0.08 sec. R_1 and R_2 are slurred. T is flat in Lead I, and upright in Lead II. The R-T segment is concave in Leads II and III.

was present at the apical area. The heart was irregular in rate, force, and rhythm, and there was a pulse deficit. The radial vessels were markedly sclerotic. A tender liver edge was palpable three fingerbreadths below the costal margin. There was pitting edema over the lower extremities extending to the midthigh. The fingers and toes showed no clubbing. Reflexes were physiological.

Course.—The patient responded very well to bed rest, diuretics, sedatives, and digitalis and was discharged after seven days to the Cardiac Clinic, which she failed to attend. On Sept. 21, 1935, one month later, she was readmitted complaining of precordial pain, dyspnea, and edema of the ankles. The blood pressure was 170/110. There was auricular fibrillation with rapid ventricular rate and a pulse deficit. Other signs were similar to those described upon the first admission. Symptomatic therapy was ineffective, and the patient expired on the third day after admission.

Autopsy (Performed by Dr. Schmidt, three hours after death).—The body was that of an adult white female, about seventy years of age, weighing about 130

pounds and appearing in fair state of general nutrition. Moderate amount of grayish hair was present upon the head and over the anterior pubes. Pupils were equal and regular, and conjunctivae, smooth and glistening. The nares and mouth were natural. The thyroid was not enlarged. The chest presented no abnormalities, and both breasts were small and atrophied; no masses were felt in either breast. The abdomen was somewhat distended, and there were several superficial, dilated veins in both upper quadrants. The extremities showed no cyanosis or clubbing, but there was considerable edema of both lower legs, extending from the ankles up to the knees.

On section, the subcutaneous fat was moderate in amount, and the musculature was flabby. The peritoneum was smooth and glistening and free of exudate. The abdominal cavity contained about 2,000 c.c. of thin, serous fluid, free from hemorrhage. The abdominal organs were apparently in their natural places.

Chest: The sternal plate was not removed owing to the limitation of permission to abdominal incision. It was determined, however, that no fluid was present in either pleural cavity.

Lungs: Both lungs were of natural size and somewhat heavier than normal. Visceral and parietal pleurae were quite separate, and the visceral pleura was glistening and free from exudate. There was a subminimal crepitation throughout. On section, homogeneous, dark red lung surface was revealed with a moderate amount of pigmentation. The surface was excessively moist, pitted upon pressure, and an excessive amount of blood and fluid could be expressed. Major and minor bronchi were natural.

Heart was greatly enlarged, weighing 505 gm. The pericardial cavity contained about 30 c.c. of thin, serous fluid, with no evidence of recent pericarditis. The pericardial surface on left anterior aspect of heart was roughened and had lost its normal glistening appearance. On opening the heart, it was found that the endocardium was smooth and glistening. The coronary sinus was somewhat dilated. The foramen ovale was patent, measuring 4 cm. in diameter. Edges were smooth. Tricuspid ring measured 13 cm., had a mild amount of sclerosis at the free margins. Chordae tendineae were thin and not fused. The right auricle appeared tremendously dilated. The pulmonic orifice measured 10 cm. Its cusps were three in number. A mild degree of fusion for about 2 mm. was found at the junction of the commissures. There was a mild degree of sclerosis at the free edge. The right ventricle was both dilated and hypertrophied, although the former condition was much more pronounced. The right ventricular chamber was approximately twice as large as the left. The right ventricular wall measured 6 mm. at the point of maximum thickness. Columnae carneae appeared flattened out. The pulmonary artery measured 10.5 cm. just distal to the pulmonic orifice, and a moderate number of yellowish plaques were present throughout. It was thin walled, dilated, and inelastic. The mitral orifice measured 8.5 cm. There was no fusion in the anterior and posterior cusps. There was a moderate amount of fatty, calcareous deposits in between the two cusps. There was no shortening or fusion of the chordae tendineae, although they appeared somewhat grayish and sclerotic. A moderate amount of sclerosis was seen along the free margin of the posterior cusp. The papillary muscles were somewhat hypertrophied, and the columnae carneae were only moderately flattened. The aortic orifice measured 7.5 cm., and the cusps were three in number. There was fusion at the commissural junctions for a distance of about 3 mm. There was some sclerosis at the base of the cusps. The left ventricular cavity was both hypertrophied and dilated, although the dilatation was very slight. The left ventricular wall measured 1.8 cm. at the point of maximum thickness. On section the cardiac muscle showed no fibrosis or fatty infiltration. Coronary ostia were patent, and traced throughout, showed a moderate amount of calcareous deposits in the wall

with visible encroachment upon the lumen. No thrombosis was seen, however. The inferior vena cava was dilated.

Aorta measured 6.7 cm. just distal to the aortic orifice, 6 cm. in the region of the arch, and 4.5 cm. in the region of the descending abdominal aorta. The ascending aorta is less than two-thirds the size of the pulmonary artery. Throughout, the wall was somewhat thicker than natural, had a reduced elasticity, and showed a moderate number of yellowish white plaques throughout. No calcification or ulceration was seen.

Liver weighed 1,450 gm. Its capsule was smooth and glistening. On section a homogeneous reddish brown liver tissue was seen. On pressure, an excessive amount of blood could be expressed. The gallbladder measured 7 cm., was free of stones,

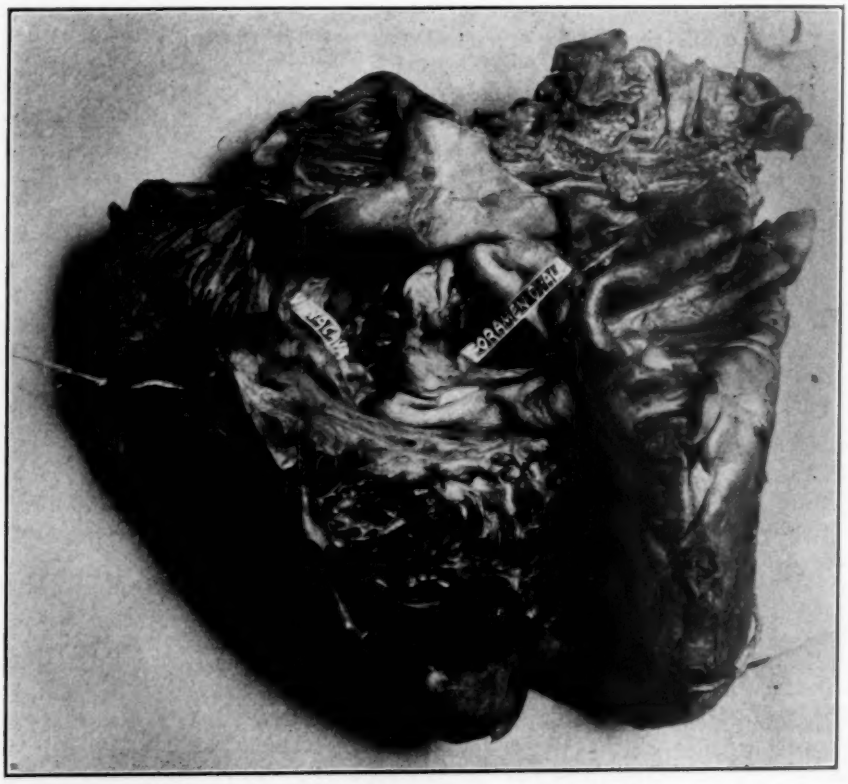

Fig. 3.—A photograph of the right side of the heart illustrating the inferior vena cava and patent foramen ovale. Note the dilated and hypertrophied right ventricle and the large right auricle.

with its mucous membrane intact. The biliary radicles were natural. Hepatic artery and portal vein showed no change.

Spleen was small, weighing 100 gm. Capsule was thick and blue in color. On section, it was rather firm, dark red, with an edematous surface, from which an excessive amount of blood could be expressed. There were numerous whitish streaks seen on the cut surface. The splenic artery and vein showed no change.

Pancreas was of natural size and, seen from the surface, presented a grayish, lobulated appearance. On section the pancreatic tissue appeared small in amount and atrophied. There were no areas of fibrosis or neoplastic infiltration.

Adrenals: Both adrenals were small, and lay in natural position. Section revealed a rather well-preserved state of the cortex and medulla.

Kidneys both were of natural size and weighed 130 gm. each. The capsule stripped with ease, revealing a surface that was reddish in color with no visible or palpable granules. There were many areas of scarring on the kidney surface. On section, the cortex was demarcated from the medulla and measured 9 mm. The kidney felt rather firm and congested. The medulla was natural. The pelves, calyces, and ureters showed no changes.

Bladder was small, contained about 10 c.c. of urine. The mucous membrane was intact, and the openings of the ureters were patent.

Gastrointestinal Tract: Esophagus was thin walled, with no ulceration or stricture. The stomach was small and contained about 20 c.c. of undigested food material. There were no hemorrhages and no visible neoplastic or ulcerated areas. Pylorus was intact. Duodenum was natural. The remainder of the small intestine was thin walled and showed no change. Large intestine was natural, free from ulceration, newgrowth, and contained a moderate amount of dark yellow feces. Rectum and anus were without change.

Genitals: Uterus was small, atrophic, measuring 2 × 2 cm. and was retroverted into the culdesac. The cervix was small and free of ulceration. On section, the uterine muscle appeared fibrotic and atrophic. The endometrium and cervical canal were atrophic. Tubes were thin walled, and the ovaries were small and atrophic and sclerotic.

Head was not examined.

DISCUSSION

The cardiovascular malformations secondary to a widely patent foramen ovale are probably best explained by the assumption that blood is shunted from the left to the right auricle. In accordance with Starling's law of the heart, the right auricle and ventricle dilate and become hypertrophied through the handling of an increased volume of blood. Because of the decreased volume of blood passing into the left ventricle and the arterial system, they become hypoplastic. The pathological physiology manifests itself clinically in the patient through pallor, a short stature, and a slight build. Cyanosis is usually not present until there is cardiac failure and the direction of the blood flow is reversed so that it flows from the right auricle to the left, "cyanosis tardive."

The physical signs as reported in the literature are extremely variable and their interpretations apparently impossible. In the case under discussion the hypertrophied conus arteriosus, dilated pulmonary artery, and increased pulmonary pressure might easily explain the accentuated pulmonic second sound, systolic thrill, and rough systolic murmur noted in the second interspace to the left of the sternum, just as these signs are found in mitral stenosis of a severe grade with marked conus enlargement. The fact that the auricles were fibrillating makes it fair to assume that they were incapable of producing such signs. Even if there had been a regular rhythm, it is hard to conceive of the auricular contraction causing a systolic thrill and a rough systolic murmur. It is interesting to note that despite a definite hypertension the electrocardiographic tracing shows the characteristic right axis deviation.

The exact cause for the cyanosis, enlarged liver, and edema is difficult to determine. Such signs frequently occur in the decompensated heart, and, though they have been described as typical of the failing heart with a large auricular defect, they are by no means pathognomonic.

SUMMARY

A case of widely patent foramen ovale in a female aged seventy-seven years is reported illustrating the characteristic physical signs, x-ray and electrocardiographic changes.

Among the features of a widely patent foramen ovale, the following may be listed:

1. Delicate physical make-up.
2. Cyanosis tardive.
3. Physical signs:
   a. Large heart
   b. Prominent conus
   c. Unusual signs at the base (not common).
4. Roentgenological features:
   a. Small aortic knob
   b. Prominent pulmonary conus
   c. Wide hilar vessels
   d. Enlarged, globular heart.
5. Electrocardiographic findings:
   a. Right axis deviation
   b. Auricular fibrillation (relatively common).

This case further serves to illustrate the rather benign nature of a large interauricular septal defect when unaccompanied by a valvular lesion.

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MASSIVE CALCIFICATION OF THE MYOCARDIUM

Report of a Case

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MASSIVE calcification of the myocardium is a very rare condition, and one of which there are not more than a dozen available reports in the literature. The following case is of interest in that there was practically complete calcification of the anterior half of the left ventricle associated with occlusion of the descending ramus of the left coronary artery, the history indicating that this occlusion took place nine years before the death of the patient.

CASE REPORT

J. W. G., a white male, aged fifty-eight years, complained of shortness of breath upon slight exertion and slight swelling of the legs during the day. At twenty-one years of age he had had inflammatory rheumatism, which left a stiff right wrist. Otherwise he enjoyed good health until September, 1926, when he was directing a crew of men in moving heavy books and equipment from the seventh floor of a building which had been so damaged by a tropical storm that the elevators could not be operated. While doing some heavy lifting during the rush, he felt something "tear in his heart." He became very weak and was unable to work and consulted a doctor who gave him treatment for heart disease. He returned to his home in Albany, Ga., in April, 1927, still weak and, according to the statement of his wife, colorless. During his illness he had continued to take digitalis prescribed at the time of his injury, which relieved a "little fullness" in his chest. During the next two years he rested, spending about eighteen hours a day in bed. Occasionally he would walk a block or two but this caused a "burning sensation in his chest, but no pain." This feeling was relieved by rest in a few minutes. In 1929 he regained his usual good color and normal weight and could walk a mile without difficulty. He had had no operations, no venereal disease.

When I first saw the patient in March, 1932, he stated that he had taken digitalis for five or six years and that it relieved a fullness in his chest better than did any drug that he had tried for the relief of pain. At this time he rested for a few days but soon felt very well and returned to his job as superintendent of a bus station. In November, 1934, I was again called to see him because of an attack of influenza. The attack was mild but left him so weak that he was unable to work for about two weeks. His health was fairly good except for a severe cough which digitalis did not relieve as well as it formerly had done. In February, 1935, he noticed considerable edema of his legs and dyspnea upon slight exertion, and he rested in bed for two weeks without consulting a doctor. He improved with rest and called at my office on March 4.

Physical examination at this time showed the cardiac impulse to be in the sixth space 1 inch outside the midclavicular line. The rate was 90; occasional premature contractions were present; blood pressure 125/85. (The patient stated that he never had had high blood pressure.) There were no murmurs, but on March 6 an intermittent gallop rhythm was noted. Moderate dullness and râles were present at the

right base. Liver dullness extended two fingerbreadths below the right costal border, and the patient complained of epigastric fullness as though he had eaten. There was moderate pitting edema of the shins. Orthopnea was never present, and, even when cardiac failure became more pronounced, the patient rested better without a pillow. The urine showed two-plus albumin with occasional hyaline casts.

Subsequent Course.—After this date the patient spent most of his time in bed, comfortable until August 1, when edema could no longer be relieved by rest, diuretics, and restricted fluids. He became progressively worse and died on Aug. 31, 1935.

The Electrocardiogram showed sinus tachycardia with rate of 130, occasional ventricular premature contractions. P_2 was notched and P-R interval 0.18 sec. QRS group showed slurring of the downstroke in Lead I, prolongation to 0.12 sec., and left axis deviation. T_1 showed high take-off and sharp inversion; T_2 was upright; and T_3 was sharply upright and greater than T_2.

Clinical Diagnosis.—Etiological, arteriosclerosis; *anatomical,* coronary sclerosis, coronary thrombosis and myocardial infarction; *physiological,* sinus mechanism, cardiac decompensation, anginal syndrome (?); *functional,* Class 3.

Autopsy Findings of Heart.—The pericardium was attached to all sides of the ventricles by numerous strong fibrous bands of adhesions. The whole anterior wall of the left ventricle was rigid, but appeared smooth and normal in shape. The percussion note was boardlike. X-ray examination of the removed specimen revealed a large area of calcification deposited in the anterior wall of the left ventricle and extensive calcification of both coronary arteries. Dr. Roy R. Kracke, of the Emory University Department of Pathology, examined the specimen and reported:

"The specimen consisted of a heart which had been fixed in formalin. It was of approximately normal shape. The pericardial surface, particularly on the anterior left ventricle, was markedly hemorrhagic with numerous petechiae and ecchymotic spots on the surface of the muscle. Also, on this same area were numerous fine fibrous adhesions. Sections of this area showed vascular channels which no doubt contributed a collateral blood supply to the left ventricle.

"The heart was slightly enlarged and weighed little more than a normal specimen. The weight was influenced by fixation to some extent. All valvular measurements were approximately normal. The aortic valve leaflets were smooth and pliable with good approximation at the commissures. The pulmonic valve was also normal. The edge of the mitral valve showed what is a questionable thickening and retraction of the free edge, although the line of closure was normal. This could have developed by fixation.

"The anterior half of the left ventricle was practically completely calcified, the area of calcification being hard, crackling, brittle, and white. It ranged in thickness from 0.5 cm. to only 3 mm. at its point of least thickness, which was near the apex. The calcified area measures 8 cm. in diameter since it is shaped like a half of a sphere. There is very little myocardial tissue in the area. The posterior half of the left ventricle is composed of normal myocardium with an occasional spot of fibrosis and calcification.

"The aorta about the coronary orifices shows a thickening with atheromatous plaques to the extent that there is almost complete closure of the left coronary opening. Examination of the left coronary shows a marked degree of calcification and intimal thickening along its entire length to the point of bifurcation where there is a complete calcified occlusion at the beginning of the anterior descending branch, with atrophy of that branch. This is an old lesion and was that which took place nine years before the death of the patient and which was followed by calcification of the part supplied by that branch.

"*Diagnosis.*—Massive calcification of the anterior left ventricle, following occlusion of the left coronary vessel at its bifurcation, this followed by development of collateral circulation through adhesions formed as a result of the infarction at that time."

COMMENT

The case of calcification of the myocardium here reported is of interest because the process was so extensive as to involve the entire anterior half of the left ventricle, because the history extended over a period of nine years, and because vascular channels were demonstrated in the pericardial adhesions, a condition similar to that found in the cases reported by Beck, Tichy, Hirschboeck, and others.

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ACUTE BACTERIAL ENDOCARDITIS IN INFANTS

Report of a Case

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CASES of acute endocarditis in infants are not often reported in the medical literature, and the diagnosis is often not made until the necropsy. Most of these cases are associated with septic conditions in other parts of the body.

It is not our purpose to review the literature, since that has been done by others. One of the more recent reviews of this subject is given by Sansby and Larson.[1] They could find reports of only five cases in infants under seven months of age. They report a case in a boy five weeks old, which followed an attack of influenza of the mother. McCartney[2] suggests that the throat was the probable source of infection in his case. Other cases associated with septic conditions at birth have been reported in infants a few days old.

CASE REPORT

This patient, a boy four months old, weighed 8 pounds and 3 ounces at birth. He was breast fed for three months and had been given supplemental feedings of milk during the fourth month. He had gained in weight normally and seemed entirely well until ten days before entering St. Luke's Hospital. At this time he refused the bottle for the first time and also had a slight cough. He was taken to the family physician who noticed a slight swelling in the region of the right parotid gland, which was suggestive of mumps. The temperature was normal, and the mother was instructed to return in a few days if the child was not improved. During the following week the mother noticed that the child had a mild fever at times but did not consider him very sick, although the glands of the neck were much larger. On the eighth day after the onset he was again taken to the family physician because of a high fever, which was found to be 105° F. One day before entrance to the hospital he was seen by one of us, who advised hospitalization and a thorough study of his condition.

On entrance to the hospital his temperature was 103.8° F.; the pulse was 130; and the respirations were 30. The following day the examinations of the otolaryngologist were negative except for the enlarged lymph glands of the right side of the neck, below the angle of the jaw and in the region of the parotid. X-ray studies of the sinuses and chest were negative. On the second day of the hospitalization the hemoglobin was 80 per cent; the red cells numbered 3,850,000; and the white count was 11,800. The urine on three examinations during the first two days was negative except for moderate amounts of acetone.

On the fourth day a few small petechiae were noticed beneath the nails of the toes and fingers. The pediatrician called in consultation suggested an x-ray study of the chest and long bones, but the report on these was negative. A blood culture grew many chains of *Streptococcus hemolyticus*. The physical examinations were negative except for the enlarged glands of the neck. The pulse was very rapid and

the fever varied from 101° to 105° F. The fever was the septic type, and death occurred on the eighth hospital day, seventeen days after the onset.

The necropsy, which was held a few hours after death, revealed many petechial hemorrhages in the skin and serous surfaces. The lymph nodes of the right side of the neck were enlarged, and those below the angle of the jaw were about 3 cm. across. The peritoneal cavity contained about 200 c.c. of clear straw-colored fluid. The lungs were congested but contained no abscesses or regions of consolidation. The heart weighed 43 gm. and many petechial hemorrhages were present in the pericardium. The right posterior aortic valve cusp was shortened and quite thick. Its surface was rough and covered with vegetations. These extended down on the endocardium of the left ventricle for a distance of about 5 mm. There were no evident changes in the other valves. The aortic and mitral valves are shown in Fig. 1. There were multiple recent infarcts in the spleen and kidneys.

The anatomical diagnosis was streptococcus septicemia with petechial hemorrhages in the skin and serous surfaces, infarcts of the spleen and kidneys, ulcerative endocarditis, and enlarged glands of the neck.

Fig. 1.

COMMENT

The symptoms in this case were those of sepsis, diagnosis of which was confirmed by the blood culture. Other foci of infection than those of the throat were sought in vain. Abnormal heart sounds were not heard on several examinations. The rapid rate of the heart and the low blood pressure in infants make it very difficult to detect disease of the heart valves in such cases. The throat was the apparent source of infection in this case.

REFERENCES

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Department of Reviews and Abstracts

Selected Abstracts

Greene, Charles W.: The Nerve Control of the Coronary Vessels With New Experimental Evidence for the Pathways of Efferent Constrictor and Dilator Neurones in the Dog. Am. J. Physiol. **113**: 361, 1935.

The data and discussions presented in this paper are condensed and briefed from a very large mass of observations on the dog. The illustrations are chosen for types and the protocols with each illustrate the method of comparison used. The major points are:

The efferent neurones to the coronary vessels are of the usual vascular antagonistic types of constrictors and dilators.

The coronary dilator neurones are of greater mass development, produce the more profound coronary reactions, and are more sensitive to stimulation.

The coronary dilator neurones are of thoracic spinal origin. They reach the heart chiefly via the stellate and the inferior cervical ganglia and the cardiac nerves arising from this region.

AUTHOR.

Kingisepp, G.: The Wash-Out of Cardiac Glucosides From the Frog's Ventricle. J. Pharmacol. & Exper. Therap. **55**: 377, 1935.

The author has investigated the reversibility of the action on the isolated and artificially stimulated frog's ventricle of the following drugs: (a) infusion of digitalis, (b) g-strophanthin, (c) ouabain, (d) digoxin, (e) scillaren, (f) k-strophanthin, (g) digitoxin.

In the case of all these drugs, washing-out produced recovery even after systolic arrest had been induced. The recovery was complete because a second intoxication followed exactly the same course as the first. The action was equally reversible when Ringer's solution or blood plasma was used, or when the drug was given to the intact frog and the arrested heart was excised and perfused. The ease with which the action could be reversed varied greatly with the different drugs.

The process of intoxication can be maintained by concentrations of glucoside far smaller than those needed to initiate intoxication.

The combination between glucosides and heart muscle resembles an adsorption process, but it is necessary to assume that hysteresis occurs.

AUTHOR.

Porter, W. B.: Diaphragmatic Flutter With Symptoms of Angina Pectoris. J. A. M. A. **106**: 992, 1936.

The case reported is unique in that the movement of the minor contractions was recorded graphically and the rate was found to be 300 or more per minute, and a study of the diaphragm under the fluoroscope showed that the contractions were bilateral, spread over the entire diaphragm and apparently rhythmic in time and amplitude. The term "diaphragmatic flutter" is most appropriate and descriptive of the observed phenomenon.

There was associated with the disturbance of diaphragmatic function severe pain in the left pectoral muscle and in the left arm and hand over an area corresponding to the eighth cervical and the first, second and third dorsal segments of the cord. Over the area of referred pain there was marked hyperesthesia, which persisted even after relief from pain followed cessation of diaphragmatic flutter.

Experience with this patient suggests that there is a syndrome which is quite similar to angina pectoris and is directly related to a functional disturbance of the diaphragm. Just how much emphasis should be placed on the syndrome is difficult to decide. It is conceivable that disturbances of the diaphragm of a similar type to those observed in this patient may be more frequent than has been realized, for the clinical symptoms and physical phenomena are most elusive and it would be quite explicable for one to class a patient as a malingerer or conclude that a coronary accident had occurred while the true nature of the illness goes unrecognized.

The diagnosis may be further confused by temporary alterations in the electrocardiogram made during the peak of a paroxysm. Just how these changes are produced is difficult to conceive, unless there occur in the myocardium nutritional alterations. The disappearance of the changes with cessation of the diaphragmatic flutter suggests a direct relationship to the disturbance of diaphragmatic function.

Experience with this patient and others who suffered from lesser degrees of what was manifestly a similar clinical condition gives evidence that the most important differential diagnostic point between Heberden's angina and the "cardiodiaphragmatic syndrome" is that the latter condition is characterized by a notable absence of substernal pain and constriction, and there is a tendency on the part of the patient to be restless, which is in bold contrast to the fixity of one undergoing an episode of angina pectoris.

AUTHOR.

Smith, Carl H.: A Method for Determining the Sedimentation Rate and Red Cell Volume in Infants and Children With the Use of Capillary Blood. Am. J. M. Sc. **192**: 73, 1936.

A method of determining the sedimentation rate of erythrocytes has been presented which employs capillary blood and is suitable for use with infants and children. The tube that has been devised constitutes in effect a reduced macrosedimentation tube in that it embodies the basic requirements of apparatus in which sedimentation tests are carried out with venous blood. Close agreement was noted in 102 comparative determinations with the method, in addition to 128 other microsedimentation tests, using blood from the heel of the infant or finger of the older child and with a standard test utilizing venous blood.

With the microsedimentation method described in this study in which 5 per cent sodium citrate was employed as anticoagulant, the average rate of settling in normal infants and children was 4.2 mm. for one-half hour and 9.1 mm. for one hour, with respective ranges of 1 to 8 mm. and 3 to 13 mm. The single determination at the end of one hour was sufficient for comparative purposes. At the conclusion of the sedimentation test, the tubes were centrifuged for one-half hour at a speed of 2,500 revolutions per minute. The range of cell volume in the normal group was from 30 to 40 per cent for citrated blood (average, 35.8 per cent). In a small group of infants and children with various infections, 95 per cent showed cell volumes of 30 per cent for citrated blood (lower level of the normal group) and over. This minimal value is tentative and may require modification with more extensive investigation.

Since the determination of the sedimentation rate has been applied chiefly as a guide to infection, various procedures have been devised to correct for the factor of

anemia which in itself markedly influences the rate. While these methods are valuable, they are subject to the criticism that the test is thereby complicated and its availability for routine clinical use limited. It has, furthermore, been emphasized that moderate grades of anemia cannot be dissociated from infection and that they usually fluctuate together. In the light of these objections and of others that are discussed, it is suggested that wherever possible the cell volume percentage be reported together with the sedimentation rate. The rate of settling may then be evaluated in accordance with the extent to which the cell volume percentage approximates the range of normal, instead of substituting for it a value derived by comparison with an arbitrary standard.

AUTHOR.

Adams, Wright: The Normal Duration of the Electrocardiographic Ventricular Complex. J. Clin. Investigation **15**: 335, 1936.

The most accurate formulas for the prediction of the duration of the electrocardiographic ventricular complex (Q-T time) from measurements of pulse interval in a series of 50 normal males and 54 normal females are: for males,

$$\overline{Q\text{-}T} = 0.1536\ R\text{-}R + 0.2462,$$

and for females,

$$\overline{Q\text{-}T} = 0.1259\ R\text{-}R - 0.2789,$$

in which Q-T = duration of electrocardiographic systole, and R-R = pulse interval. A table is provided which simplifies the use of these formulas.

The use of age, height, and weight of the individual, and height of the T-wave and axis of the electrocardiogram does not appreciably increase the accuracy of prediction of the duration of the electrocardiographic ventricular complex.

Other workers have found the duration of the electrocardiographic ventricular complex to be shorter for corresponding pulse rates. The reason for this difference is not apparent, but several possible explanations are discussed.

AUTHOR.

Hamburger, Walter W., Katz, Louis N., and Saphir, Otto: Electrical Alternans. J. A. M. A. **106**: 902, 1936.

In a case of transient isolated electrical alternans, autopsy revealed an anomalous distribution of the right coronary artery with a calcified plaque markedly narrowing its mouth, generalized coronary arteriosclerosis, and multiple microscopic myocardial infarcts. In a second case of possible isolated electrical alternans, autopsy revealed multiple minute carcinomatous metastases within the myocardium and in the blood vessels of the heart. In the instance of alternans in auriculoventricular conduction no similar clinical report was found in the literature. It seems likely that the anatomical lesions in the first two instances, by leading to malnourishment of fractions of the heart, were responsible for the electrical alternans. They are, therefore, both of the coronary type of Kisch. The appearance of electrical alternans in instances in which the myocardial lesions are small and scattered may be significant.

A search of the literature revealed the rarity of isolated electrical alternans, the first case being the first described in this country and the first published with necropsy data.

The transitory nature of electrical alternans is demonstrated in our first case. There is a grave prognostic significance of electrical alternans.

While alternans of the heart may appear in several forms, there is evidence to show that fundamentally the mechanism is identical in all instances; namely, alternation of activity of portions of the heart. The form taken by the alternans will depend on the distribution of the alternating portions of the heart. The

transient character of electrical alternans emphasizes the need for closer scrutiny of electrocardiograms. The gravity of alternans and the fact that it sometimes appears only in the electrical form emphasizes the need of becoming more "alternans conscious." If more attention were paid to electrical alternans, probably many more instances would be found.

AUTHOR.

Maher, Chauncey C.: The Effect of Two Water-Insoluble Squill Glucosids Upon the Electrocardiogram. Am. J. M. Sc. **192:** 41, 1936.

The effects of squill glucosides upon the electrocardiogram appeared to be characteristic and fairly consistent, particularly upon the R-T and S-T segments. The recorded changes of concavity and convexity produced were similar to those produced by digitalis as reported by Cohn and Pardee. In those patients whom we studied with both urginin and digitalis the changes produced were similar with equivalent amounts of each drug over equal periods of time.

There was a wide variation in the degree of effect produced in different patients, implying a variable amount of absorption of the ingested drug, a difference in the response of the patient, or other unknown factors.

In therapeutic doses, which is a relative term varying with each patient, the effects of urginin, like those of digitalis, appeared to be limited to an effect upon the R-T or S-T segment, slight prolongation of the P-R interval, and occasional extrasystoles.

In patients intolerant to the medication, the effects of overdosage appeared to be the production of frequent extrasystoles, marked prolongation of the P-R interval and the production of auricular fibrillation.

AUTHOR.

Master, A. M., Jaffe, H. L., and Dack, S.: Undernutrition in the Treatment of Coronary Artery Disease (Particularly Thrombosis). Effect on the Basal Metabolism and Circulation. J. Clin. Investigation **15:** 353, 1936.

The effect of a low calorie diet (800 calories) on basal metabolism was studied in twenty-eight patients with coronary thrombosis and in fourteen with angina pectoris, whose control basal metabolic rate was within normal limits.

In thirty-one patients (74 per cent) the basal metabolic rate was lowered 15 to 35 per cent; such a drop was considered significant. In six patients, the basal metabolic rate fell 10 to 14 per cent, and in five, less than 10 per cent. The time required for the basal metabolism to drop was from two to four weeks. A similar period was required for its return to normal following the resumption of a regular diet. The body metabolism is determined for several weeks by the previous state of nutrition. Following a period of undernutrition, a subsequent period produces a more rapid and profound drop in basal metabolism. The loss of weight necessary to attain a significant fall in basal metabolism averaged 6 per cent of the initial body weight. The following factors tended to prevent a significant fall in basal metabolism: insufficient loss of weight, cardiac failure, upper respiratory infection, and repeated attacks of angina pectoris.

No ill effects resulted from the low metabolism induced by prolonged undernutrition of from three to twelve months' duration. The blood cholesterol, sugar, and protein were unaffected. Graduated increases in diet to 1,200, 1,500, and 2,000 calories often resulted in corresponding rises in basal metabolism. The drop in basal metabolism is not accompanied by such evidences of hypothyroidism as myxedema, diminished blood velocity, and hypercholesterolemia. Vital capacity is not affected.

The lowered basal metabolism had a beneficial effect on the cardiovascular system, resulting in slowing of the pulse rate, decrease in blood pressure and pulse pressure and diminution of the cardiac output and work of the heart. A low calorie diet often relieves the symptoms of heart disease.

AUTHOR.

Levy, Robert L., and Bruenn, Howard G.: Acute, Fatal Coronary Insufficiency J. A. M. A. **106:** 1080, 1936.

There is a group of patients with atherosclerosis of the coronary arteries to whom death comes suddenly and in whose coronary vessels, at necropsy, no fresh thrombus is found. The syndrome may be designated "acute, fatal coronary insufficiency."

The clinical and pathological features of twenty-four cases falling into this category have been studied. Records of 352 other cases of coronary sclerosis, with and without thrombosis, have been similarly studied and used as a background for comparison.

In approximately 12 per cent of the fatal cases of coronary sclerosis without thrombosis, death occurred suddenly. If thrombosis had occurred, death was sudden in 33 per cent. The presence of thrombosis thus almost tripled the likelihood of sudden death. But thrombosis of a coronary artery was rarely if ever the immediate cause of death in these patients. It increased the liability to acute coronary insufficiency by further reducing the functional capacity of an already impaired coronary system.

Nonfatal attacks of various sorts in patients with coronary sclerosis may be regarded clinically as intermediate between the ordinary bout of anginal pain or its equivalent and a fatal seizure. It is probable that many of these attacks are due to minor degrees of acute coronary insufficiency without occlusion.

AUTHOR.

Willius, Fredrick A.: Life Expectancy in Coronary Thrombosis. J. A. M. A. **106:** 1890, 1936.

In this study of 370 cases of coronary thrombosis, in 71.9 per cent the thrombosis occurred when the patients were between the ages of fifty and seventy years. No patients were less than thirty years of age; the incidence in the fourth decade of life was 1.6 per cent, while 17 per cent of the patients were in the fifth decade. There was a great predominance of males over females; the ratio was 7:1.

Solitary coronary occlusion occurred in 80.3 per cent of the cases; two episodes occurred in 17 per cent, three attacks in 2.2 per cent, and four episodes in 0.5 per cent of the cases.

Death directly attributable to the heart occurred in 51.6 per cent of the cases, while other diseases such as pneumonia, cancer, and nephritis accounted for the death of 2.7 per cent of patients. The patients surviving at the conclusion of the study comprised 45.7 per cent of the group.

Of the cardiac deaths 36.6 per cent were ascribable to coronary thrombosis; gradual cardiac failure accounted for 51.9 per cent, and sudden death of uncertain mechanism for 11.5 per cent.

While the incidence of females in this study was relatively small (12.4 per cent) their cardiac death rate was considerably greater than among males: females 63 per cent and males 50 per cent.

There was no correlation between the duration of pain in coronary thrombosis and death or survival.

The cardiac death rate increased progressively with recurrent coronary thrombosis. Among cases of solitary coronary occlusion the cardiac mortality was 47.5 per cent,

among cases in which there were two attacks 69.8 per cent, and among those in which three attacks occurred 75 per cent.

The patients living at conclusion of this study comprised 45.7 per cent of the group. Of these, 42.6 per cent reported themselves to be in good health, 23.1 per cent were well while living a restricted life, 28.9 per cent had recurrent anginal attacks, 3.6 per cent had congestive heart failure, and 1.8 per cent had had cerebral vascular accidents.

AUTHOR.

Alvarez-Moulia, A.: Congenital Stenosis of Aortic Orifice. Arch. urug. de med., cir. y especialid. **7**: 499, 1935.

The author has had opportunities to study several cases of this congenital chronic disease in which most of the patients reached adulthood without their symptoms' needing special treatment. After a study of this disease some clinical, radiological and electrocardiographic symptoms may be added to the clinical picture already known.

The great clinical similarity of all the cases is striking. Each one shows the great degree of hypotrophy or aortic dwarfishness; this causes an inferior bodily development which would seem to be the result of the lesion's interfering with the blood supply of the great circulation. This interference constitutes an impediment for the development of organs during the growing period. The mental defectiveness, according to the author, is attributed to a pathogenic process resembling the former. There is, also, an hypotrophy of vessels revealed by the oscillometric study of the patients, due to the same pathogenic process to which the dwarfism is attributed.

The comparative examination of the electrical records obtained from the patients studied establishes fitting characteristics of the electrocardiograms. They will be: R_3 R_1 R_2 form accompanied with "high tension or voltage" widening of the QRS space, slight crochetage of the R-wave in Lead III and above all as the most important element, an inversion of the ventricular deflection T in the three classic leads. These electrocardiographic signs have special interest since electrocardiograms obtained in the valvular diseases are more variable and contradictory.

The explanation of the stability of the different deflections, according to the author, is that the permanent intraventricular tension values have, on the whole, a great importance in the formation of the proper physiognomy of each electrical record. The continued action of the cardiac muscle from birth against the intraventricular tension causes an adaptation of its contracted state and tonicity. The ventricular preponderance, the muscular hypertrophy, and above all the special manner of the distribution of the final elements of the conduction apparatus will be in consequence to this. The latter elements of the "intraventricular conduction" will form the special type of electrocardiogram.

AUTHOR.

Sendroy, Julius, Jr., and Schultz, Mark P.: Studies of Ascorbic Acid and Rheumatic Fever. I. Quantitative Index of Ascorbic Acid Utilization in Human Beings and Its Application to the Study of Rheumatic Fever. J. Clin. Investigation **15**: 369, 1936.

The urinary excretion test for the adequacy of ascorbic acid nutrition has been improved and placed upon a quantitative basis by a chemical and clinical study of the various factors affecting the final results. Applied to a comparison of patients with rheumatic fever and control subjects, the results of this method do not support the concept that a condition of ascorbic acid deficiency is a predisposing factor in the causation of this disease.

Through digestive disturbances, patients with rheumatic fever evidently may develop a real hypovitaminosis on an ordinarily adequate diet. One would expect in such patients that the tissues might be depleted not only of ascorbic acid but of other vitamins and essential food constituents of which there may not be large reserves in the body. However, even if we assume, contrary to the evidence of our experiments, that it is simply ascorbic acid deficiency that is associated with every case of rheumatic fever, it seems much more reasonable to regard the train of events, including digestive disturbances, leading to such depletion of the tissues, as caused by an infectious process, rather than to think of the ascorbic acid deficiency as initiating the infection. It seems certain that the factor of infection is present in all cases of rheumatic fever, whereas the signs of ascorbic acid subnutrition, if present, are probably incidental. Furthermore, it should be noted again that such signs of deficiency as have been found are only relative and not absolute. It has already been pointed out that the average results set up too high a standard of normality so that degrees of ascorbic acid deficiency, relative to the control patients previously on diets of about 100 mg. ascorbic acid daily, would be exaggerated in the direction of ratings too low for ascorbic acid nutrition. When all of these factors are taken into consideration, it is difficult to accept subclinical scurvy as an etiological agent in rheumatic fever.

AUTHOR.

Schultz, Mark P.: Studies of Ascorbic Acid and Rheumatic Fever. II. Test of Prophylactic and Therapeutic Action of Ascorbic Acid. J. Clin. Investigation **15**: 385, 1936.

Two comparable groups of rheumatic children, one of them receiving daily doses of ascorbic acid, were observed at intervals during late winter and early spring. As indicated by tests of capillary permeability, the development of subclinical scurvy was prevented in the treated group, but the incidence of active rheumatic fever was not favorably affected by this medication.

The clinical manifestations of acute rheumatic fever were not demonstrably affected by the oral or intravenous administration of ascorbic acid over periods of several months. Large doses of orange juice were also ineffective.

These data are additional evidence that ascorbic acid deficiency is not a necessary factor in the etiology of rheumatic fever.

AUTHOR.

Pickering, G. W.: The Effect of Introducing Blood From Patients With Essential Hypertension Into Other Human Subjects. Clin. Science **2**: 185, 1936.

The changes in arterial blood pressure produced in anemic subjects by transfusion of blood from patients with essential hypertension are very small and are no greater than those produced by transfusion of an equal volume of normal blood. This result is opposed to the idea that the raised blood pressure in essential hypertension is due to excess of pressor or deficit in a depressor substance in the circulating blood.

E. A.

Pickering, G. W., Kissin, M., and Rothschild, P.: The Relationship of the Carotid Sinus Mechanism to Persistent High Blood Pressure in Man. Clin. Science **2**: 193, 1936.

The idea that certain forms of human hypertension might be due to an interference with the carotid sinus and depressor reflexes arose from the demonstration that high blood pressure could be produced in the experimental animal by denervating

the carotid sinus and arch of the aorta. A comparison of the chief features exhibited by patients suffering from the common forms of persistent hypertension with those exhibited by the animal with this form of experimental hypertension is instructive, for it reveals differences that are so striking as to leave no doubt as to the essentially different origin of human and experimental hypertension. Thus tachycardia is invariable in the experimental hypertension and exceptional in human hypertension; compression of the carotid artery below the sinus gives no response in the animal and a definite response in man; sensory stimuli produce a fall of blood pressure in the animal and a rise in man; in sleep the blood pressure falls to normal in the animal and remains elevated in man; and last, characteristic histological changes in the arterioles are absent in the experimental and usually present in the human form. It is not to be denied that there may be examples of hypertension in man which are similar in origin to the experimental form. Such cases must be uncommon and the authors are not satisfied that the evidence for their existence is adequate.

The function of the carotid sinus mechanism was tested in four groups of human subjects: (1) young adults with normal blood pressure, (2) elderly subjects with normal blood pressure, (3) patients with chronic nephritis and hypertension, (4) patients with essential hypertension. The differences in the response to carotid sinus compression shown by the various groups seemed to be entirely accounted for by differences in the initial levels of blood pressure and by differences in the degree of sclerosis of the large arteries. Digital obliteration of one carotid artery below the sinus produced, in all subjects with normal and high blood pressure, rises of blood pressure and pulse rate that were greater than those produced by control pressures on the neck and femoral artery.

E. A.

Pickering, G. W., and Kissin, M.: The Effects of Adrenaline and of Cold on the Blood Pressure in Human Hypertension. Clin. Science **2**: 201, 1936.

No evidence was found that patients with chronic nephritic hypertension are abnormally sensitive to adrenalin. Evidence was presented against the view that essential and nephritic hypertension are due to hyperadrenalinemia. The suggestion that a relatively large rise of blood pressure in response to a cold stimulus is peculiar to potential or developed cases of essential hypertension is unconfirmed; however the series is too small to exclude the possibility that the rise of blood pressure is, in general, greater in subjects with hypertension than in those of similar age with normal blood pressures.

E. A.

Veal, J. Ross: Vascular Changes in Intermittent Claudication. With a Note on the Value of Arteriography in This Symptom Complex. Am. J. M. Sc. **192**: 113, 1936.

The theories of the origin of pain in intermittent claudication are briefly reviewed.

An arteriographic study of 15 carefully selected cases of intermittent claudication is reported.

Attention is called to the fact that in 3 cases of undetermined etiology the radiographic evidence shows an entirely different type of lesion from that noted in the other twelve cases, in which the etiology was arteriosclerotic.

Arteriographic evidence is adduced to support the contention that the pain in intermittent claudication is not due to arterial spasm.

An illustrative case is cited to show that the improvement which follows heat, exercise, and similar measures in intermittent claudication is not due to any notable change in the vascular supply but presumably to the temporarily increased nutrition of the parts which is achieved by this form of therapy.

AUTHOR.

Kampmeier, R. H.: Aneurysm of the Abdominal Aorta: A Study of 73 Cases. Am. J. M. Sc. **192**: 97, 1936.

Aneurysm of the abdominal aorta is a relatively uncommon lesion. From the records of Charity Hospital for the past thirty years there have been selected sixty-eight such cases in which the diagnosis could not be questioned. This group is the largest which has ever been collected from any one institution. The etiological factors in the production of aneurysm of the abdominal aorta have been discussed, and the clinical features have been described. Roentgenological findings of great importance in diagnosis have been emphasized. Diagnosis of abdominal aortic aneurysm involves the consideration of a number of conditions and may be difficult or even impossible. Prognosis in this lesion is poor, the majority of patients dying within six months from the onset of symptoms. Death is usually sudden and due to rupture of the aneurysm. The necropsy findings in thirty-eight cases have been presented.

AUTHOR.

Cohn, Isidore: Arteriovenous Aneurysm of the First Portion of the Right Subclavian Artery and Innominate Vein; Report of a Case Successfully Operated Upon. Ann. Surg. **103**: 964, 1936.

A case of arteriovenous aneurysm of the first portion of the right subclavian artery and innominate vein is reported. The patient was not conscious of the existence of the aneurysm for nearly eighteen months after the original injury. The bradycardic phenomenon was not present. The heart was only slightly enlarged. Pulsations did not return to the radial and brachial arteries after operation. In spite of this, the collateral circulation was adequate. The value of pavaex treatment as an adjunct in developing collateral circulation was demonstrated. The operation consisted of ligation of the internal jugular vein, ligature of the right subclavian artery and the innominate vein on either side of the fistula and obliterative suture of the vein and artery at the site of the fistula. Cure of the aneurysm resulted.

E. A.

Lewis, Thomas, and Pickering, G. W.: Circulatory Changes in the Fingers in Some Diseases of the Nervous System, With Special Reference to the Digital Atrophy of Peripheral Nerve Lesions. Clin. Science **2**: 149, 1936.

Disuse, whether resulting from lesions of the motor nerves, from fixation of the joints or tendons, or from psychical disturbances, leads to a diminished circulation through the skin of the immobilized part. After loss of sympathetic supply, there is some regaining of tone by the vessels of the affected limb, but the skin remains in general warmer than the symmetrical normal skin. After combined loss of motor and sympathetic supply, as in cases of long-standing anterior poliomyelitis subjected to sympathectomy, the affected limb is in general warmer than the unaffected. Section of a mixed peripheral nerve leads first to abnormal warmth, but soon to persistent coldness of the denervated skin. The change from

warm to cold skin seems to correspond in time with degeneration of the sensory fibers. The reduction in blood flow through the skin after section of a mixed nerve is due chiefly to loss of the posterior root fibers, partly to regain of vascular tone after loss of sympathetic supply, and partly to muscular inactivity consequent on motor nerve loss. The possibility of organic vascular change in the digital vessels in long-standing cases of peripheral nerve section is also considered.

The nutritional changes in the skin, subcutaneous tissues, and bones are described in a number of patients with lesions of the nervous and locomotor systems. These changes may all be explained by disuse, defects in blood flow, and sensory loss, and it is unnecessary to assume in explanation any "trophic" influence of the nervous system on these structures.

E. A.

Warfield, Louis M.: Circulatory Failure. J. A. M. A. **106**: 892, 1936.

It is not the heart that fails in acute infections; the peripheral circulation collapses so that the heart has no blood finally to pump. The condition is analogous to secondary shock. The heart usually becomes smaller in acute infections until just before death, when it dilates because of anoxemia.

Digitalis is not a useful drug in these cases of peripheral circulatory failure. Measures to increase blood volume such as intravenous administration of sufficient quantities of physiologic solution of sodium chloride, dextrose, or Ringer's solution or direct or indirect blood transfusions should be used. Drug therapy, up to the present time, is limited to strychnine, pitressin, and epinephrine. Whenever there is evidence of anoxemia (cyanosis of the nail beds, and so on) oxygen should be given in sufficient quantities to overcome the cyanosis.

Patients with severe infections cannot all be saved, but it is believed that more can be saved by using the procedures outlined than by the methods still described in textbooks.

AUTHOR.

Goldberg, Samuel J.: The Use of Calcium Gluconate as a Circulation Time Test. Am. J. M. Sc. **192**: 36, 1936.

The arm-to-tongue circulation time, a relative index of the rate of blood flow through the lungs, is a useful test of the functional efficiency of the circulation. The velocity with which the blood flows through the lungs is a composite result of the oxygen demands of the body and the capacity of the heart and blood vessels to propel the blood to meet such demands.

A simple method is described which lends itself to general use, and the results in 156 normal and pathological cases are reported. The calcium gluconate method gives normal readings varying from 10 to 16 seconds, with an average arm-to-tongue circulation time of 12.5 seconds.

Hyperthyroidism increases the velocity of the blood flow, and cardiac failure markedly slows it. In myxedema and hypothyroidism there is a slowing of the circulation in proportion to the fall in metabolism. The test is helpful in the differentiation of edema of cardiac or renal origin, and may be of assistance in distinguishing between cardiac and bronchial asthma. The calcium gluconate test is approximately accurate and easy to perform. No untoward effects have been observed, nor has there been any thrombosis or tissue damage in a single instance.

AUTHOR.

Hickman, J., Livingstone, H., and Davies, M. E.: Surgical and Anesthetic Risk in Cardiac Disease. Arch. Surg. **31**: 917, 1935.

Since there were only six deaths due to cardiac disease and two deaths due to pulmonary disease related to the surgical intervention and anesthesia in 336 patients who underwent 345 operations, the resulting mortality of 2 per cent indicates that as a group patients with cardiac disease are fairly good surgical risks.

Angina pectoris, coronary occlusion, decompensation, hypertension and thyrotoxic heart disease are, in the order named, the most serious diseases with which one has to deal.

Contrary to the belief of several authors, inhalation anesthesia, particularly ethylene-oxygen anesthesia, is safe when a high percentage of oxygen is used and asphyxia or struggling is avoided. Ethylene-oxygen and local anesthesia have given the most satisfactory results in this series of cases. The use of spinal, ether or nitrous oxide-oxygen anesthesia has increased the incidence of postoperative complications and death.

AUTHOR.

Shipley, Arthur M., and Winslow, Nathan: Purulent Pericarditis. Arch. Surg. **31**: 375, 1935.

Purulent pericarditis is an abscess and, like a collection of pus anywhere else, should be treated by incision and adequate drainage. Too much cannot be said in favor of early operation, but it should be remembered that late operation does not rob the patient of the hope of cure. Operative treatment should yield a cure in 50 per cent of the cases.

The best approach is the costoxiphoid route with resection of the left seventh, sixth, and fifth costal cartilages together with a portion of the sternum, when more room is needed. Therapeutic aspiration may be used, on occasion, with profit, but it has no curative value.

There are three chief factors that govern prognosis: (1) the time of the operation; (2) the type of the organism; and (3) the original condition of which the pyopericardium is a complication. Purulent foci elsewhere, unless detected early and promptly remedied, render the prognosis less favorable.

In the past seven years there has been no appreciable improvement in the operative mortality rate. Pyopericardium is a disease of youth. Eighty-three per cent of the patients are under thirty years of age. Seventy per cent of the patients have been males, and 30 per cent have been females. Troublesome postoperative adhesive pericarditis does not occur as often as it is generally supposed.

AUTHOR.

Winslow, Nathan, and Walker, W. Wallace: End-to-End Vascular Anastomosis: An Experimental Study. Ann. Surg. **103**: 959, 1936.

After exposing the vessel, the circulation is arrested by bulldog clamps. The adventitia is grasped between a finger and thumb, drawn tight and cut off at a level with the rest of the vessel. Blood is gently stripped out of the lumen of the vessel, which is kept moist by washing with normal saline solution. The wall of the divided vessel is grasped near its open end with a fine smooth-mouthed pick-up forceps and four sutures of fine silk inserted through the margin of the divided vessel at equidistant points. These sutures are tied to the edge of the vessel with a single knot, and their free ends passed through the ring of bone. The ring is slipped over the vessel and a sufficient length of the vessel allowed to

protrude to cover the bone. The bone is held firmly in place by a barbed holder slipped between it and the end of the vessel to be cuffed. The redundant end of the stump is then rolled back over the bone by gentle traction upon the guy or stay sutures. The end of the distal stump is now slid over the segment of vessel which houses the ring of bone and, together with the cuff, is held securely in place on the bone by a temporary encircling ligature. At this stage of operation, the circulation is reestablished by removing the bulldog clamps. The holder is also removed. A ligature of fine silk is then introduced through each of the four holes in the ring and passed through the two ends of the divided vessel. These ligatures are anchored to the free margin of the ring of bone, after which the encircling ligature is removed and the guy sutures cut away.

By this technic the authors have had vessels with open lumina nearly a year after being anastomosed.

E. A.

Bower, J. O., and Mengle, H. A. K.: The Additive Effect of Calcium and Digitalis: A Warning, With a Report of Two Deaths. J. A. M. A. **106**: 1151, 1936.

Two deaths occurred following the intramuscular administration of digitalis and the intravenous injection of calcium gluconate chloride.

The manufacturers of calcium gluconate or chloride should preface their literature with a warning relative to the additive effect of calcium and digitalis when given simultaneously.

AUTHOR.

Wilson, H., and Roome, N. W.: Passive Vascular Exercise: Observations on Its Value in the Treatment of Peripheral Vascular Disease. J. A. M. A. **106**: 1885, 1936.

As a result of treating twenty-three individuals with varying amounts of passive vascular exercise in the pavaex apparatus, the authors found little improvement definitely attributable to the specific therapy.

Twelve arteriosclerosis patients were given from 17 to 111 hours; five were slightly benefited; the rest showed no change. Only two of the eight patients with thromboangiitis obliterans were definitely benefited. One of three patients with major embolisms recovered, the authors being doubtful that the pavaex treatments affected the outcome one way or the other.

L. H. H.

Book Review

LE TONUS CARDIO-VASCULAIRE ET L'ÉPREUVE AMPHOTROPE SINO-CAROTIDIENNE. By D. Daniélopolu, Paris, 1935, Masson et Cie., 200 pp. and 78 figures.

Since the mechanism of the carotid sinus reflex was worked out by Hering in 1927 and further elaborated by Heymans and his associates (1929), the literature has abounded in contributions to the mechanism of the working of the carotid sinus. To the literature of this subject Daniélopolu and his associates have made many recent contributions. The volume which Daniélopolu has now written brings together the views of this group of investigators about the functions of the carotid sinus. These views are at times at variance with those of other contributors to this subject, but it appears most frequently to be a question of interpretation, for the experimental observations are recorded and their deductions made; the data which have been reported by others are reinterpreted to bring them into line with their own notion of the "amphotropic" nature of the carotid sinus. The reader, however, is free to draw his own conclusions.

The book is very well planned. The historical section is well done. Then follows a discussion of the "mechanism of the cardio-vascular tone," then a description of technics the author and his associates used (electrocardiograms and blood pressure measurements) followed in turn by an exposition of the amphotropic nature of the carotid sinus in the normal subjects and then, in turn, by its application to pathological situations, closing with a summary. It is surprising that no mention is made of Bronk's contributions to the physiology of the carotid sinus.

Naturally the clinician turns with interest to the section dealing with pathological situations. I think it is here that one finds the greatest difficulty in agreeing with the author, for he has found it too easy to explain phenomena of disease by calling into play the carotid sinus mechanism: changes interpreted as associated with valvular lesions, with myocardial disease, with emphysema, with angina pectoris; the mechanism of arterial hypertension (essential), of paroxysmal hypertension, of the cardiac irregularities, of pulsus alternans, all are brought into line with the working of the carotid sinus.

Those interested in cardiac physiology and disease will find this monograph suggestive and stimulating.

H. J. S.